Revised assessment of Bovine Spongiform Encephalopathy (BSE) risks associated with the importation of certain commodities from BSE minimal risk regions (Canada)

Veterinary Services

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Table of Contents

List of Tables and Figures

Executive Summary

On January 4, 2005, the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) published in the *Federal Register* a final rule (70 FR, Docket No. 03-080-3, pages 459-553) to amend the regulations regarding the importation of animals and animal products to 1) establish a category of regions that present a minimal risk of introducing bovine spongiform encephalopathy (BSE) into the United States (BSE minimal risk regions) via live ruminants and ruminant products and byproducts, and 2) add Canada to that category. That rule also established conditions for the importation of certain live ruminants and ruminant products and byproducts from such regions.

We are now amending the regulations to allow the importation of certain additional commodities from BSE minimal risk regions – currently, only Canada. This risk assessment evaluates the potential BSE risk associated with the amended regulations. The risk assessment indicates that the actions outlined in the final rule will continue to protect against the introduction and establishment of BSE into the United States.

Commodities discussed in this risk analysis reflect those that, in accordance with the World Organization for Animal Health (OIE) guidelines, can be safely traded under certain conditions. APHIS is allowing the importation of 1) live bovines (cattle and bison) that were born after the date when a ruminant-to-ruminant feed ban was effectively enforced; 2) blood and blood products collected under certain conditions; and 3) bovine small intestine, other than distal ileum, under certain conditions.

This risk assessment includes both quantitative and qualitative evaluations of the animal health risks associated with these products and the likelihood that these products imported from minimal risk regions (Canada) would introduce BSE infectivity into the United States and expose the U.S. cattle population. The analysis uses the approach recommended by the OIE (*Terrestrial Animal Health Code* Section 1.3 Risk Analysis) for trade-related animal health risk assessments, which focuses on determining likelihood of release, likelihood of exposing susceptible animals given release, and the magnitude of consequences given release and exposure.

The analysis includes consideration of the effects of mitigations for each of these commodities as follows:

1. Live cattle and bison: live bovines were born on or after March 1, 1999.[1]
2. Blood and blood products:
   For all blood:
   a. the blood is collected in a closed system.
   For blood collected at slaughter:
   b. the slaughtered animal passed ante-mortem inspection and
   c. was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or a pithing process.

[1] This analysis includes animals under 30 months of age, as well as older animals that will be allowed entry under this amended regulation.

For fetal bovine serum:

d. the dam passed ante-mortem inspection and was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or a pithing process.
e. the uterus is removed from the dam's abdominal cavity intact and taken to a separate area away from the kill floor.

For blood collected from live donors:

f. the donor must be free of clinical signs of disease.

3. Bovine small intestine: small intestine must exclude the distal ileum by removing at least 80 inches of the uncoiled and trimmed small intestine as measured from the cecocolic junction and progressing proximally toward the jejunum.

The analysis uses both qualitative and quantitative methods for various parts of the assessment. As part of the release assessment, we use quantitative methods to estimate the current prevalence of BSE in the standing adult cattle population in Canada. We use qualitative methods to describe the most likely outcomes of the release assessment. In the exposure assessment, we again combine both qualitative and quantitative methods. In those instances where we either cannot numerically represent the expected outcome, or where the numbers would be so low as to prevent their use in further calculations, we qualitatively assess the possible exposure.

The BSurvE model with modifications is used to quantitatively estimate the current prevalence of BSE in the standing adult cattle population of Canada. This model cannot predict future changes in prevalence. Thus, it was necessary to qualitatively evaluate the available evidence to anticipate how the prevalence may change over time. Based on evidence from the United Kingdom (UK) and Europe about the effects of a feed ban, as well as on the results of simulation models, we expect that the prevalence of BSE in Canada will decrease continuously over the next several years. A key assumption underlying this expectation is that an effectively implemented feed ban, in conjunction with appropriate import controls, will be sufficient to eventually eradicate BSE in a country's cattle population. Although the BSE epidemic curve in Europe exhibits a long tail, the assumption of eventual eradication of the disease resulting from a feed ban is consistent with epidemiologic simulation modeling predictions.

Although this scenario is the most likely, because we cannot provide an accurate prediction for the rate at which we might expect the already low prevalence to decrease, we cannot numerically represent the expected annual release over the time period of the analysis. Therefore this scenario is described qualitatively.

To provide sufficient numeric input for the quantitative exposure assessment model, we make the assumption that BSE prevalence in Canada remains constant over the next twenty years. We acknowledge that this quantitative evaluation is actually a less likely scenario, and may over-estimate the overall risk. For this assessment, we assume that the August 2006 prevalence, calculated using the Bayesian Birth Cohort (BBC) model, remains constant over the next 20 years. Even though the BBC model may underestimate the current prevalence of BSE in Canada (an alternative current prevalence estimate is

provided for sensitivity analysis), we expect that assuming it to remain constant at this level over the next 20 years would still overstate prevalence during the time horizon of the analysis. This assumption of constant prevalence, combined with the estimates of projected cattle imports from Canada, provide the values for release of infected live animals in this less likely scenario. This numeric input is necessary for the quantitative model used to inform the exposure assessment.

The exposure assessment for live animals qualitatively indicates that, because the most likely expectation is that Canada's prevalence will decrease over time, and because of the barriers to BSE transmission in the United States, the likelihood of BSE exposure and establishment in the U.S. cattle population as a consequence of imports from Canada is negligible. In our quantitative consideration of less likely scenarios, the exposure assessment evaluates the impact of the numbers of infected animals imported, assuming constant BSE prevalence in Canada, on the likelihood of U.S. cattle exposure to BSE. We base our evaluation on the Harvard Center for Risk Analysis BSE simulation by Cohen et al., updated to incorporate new evidence (e.g., regarding misfeeding, proportion of animals that are rendered and the additional poultry litter pathway) and domestic regulations, and the proposed changes considered here. In order to provide time for several potential infectivity cycles, this model tracks BSE release and exposure in the United States over 20 years. In the current analysis, it indicates that even with risk-inflating assumptions about the possible level of infectivity released into the United States, there is little spread of disease to U.S. animals. Assuming the less likely scenario of constant BSE prevalence in Canada, the model predicts that over the 20 years of the analysis, importation of approximately 19 infected animals leads to approximately two U.S. cases as secondary spread. Since most animals are slaughtered during the lengthy incubation period, only 0.67 of all 21 infected animals predicted by the model would live to show clinical signs of BSE.

Considering evidence provided in the consequence assessment, we expect that even the unlikely scenario evaluated in the quantitative release and exposure assessments results in negligible economic costs of BSE. Although human health is not the focus of this assessment, we note that the quantitative model, which includes multiple sources of risk over-estimation, indicates a negligible level of infectious agent that may be potentially available for human exposure. We conclude that the likelihood of BSE establishment and the impacts of cases that may occur even without establishment as a result of importation of live bovines under the conditions specified are negligible.

The likelihood of release and exposure via blood and blood products, and bovine small intestine other than distal ileum, were evaluated qualitatively. We conclude that the joint likelihood of BSE release and subsequent exposure of bovines to infectivity from either of these commodities is negligible. We further conclude that this negligible likelihood would result in few or no U.S. cases of BSE. Therefore, the consequences and resulting risk of the importation of these commodities are negligible.

Revisions following peer review and other updates

Following Office of Management and Budget (OMB) guidance (OMB 2004), this risk assessment was peer reviewed by four experts in the fields of BSE, modeling, quantitative risk assessment and its application to regulatory decision making, and international health standards. The charge to reviewers, peer review report (RTI 2007) and our response are available at http://www.aphis.usda.gov/peer_review/peer_review_agenda.shtml. In summary, the reviewers found that the methods used in the risk assessment (1) were scientifically rigorous in terms of using existing literature and models appropriately and making sound assumptions and (2) adhered to international risk assessment standards. The reviewers also agreed with the conclusion that the likelihood of establishment of BSE in the U.S. cattle population is negligible.

In addition to supporting the methods, evidence, and conclusions presented by the APHIS risk assessment, the reviewers made several suggestions for the document's improvement. In this revised version of the risk assessment prepared for publication with the final rule, we have incorporated clarifications and updates based on these suggestions.

One of the issues considered in response to peer review was the potential impact of additional BSE cases detected in Canada on our risk estimates. In a new "Updates" section of this assessment we present analyses designed to assess the sensitivity of our results to such updates in available data. In addition to considering the additional cases, as suggested by peer review, we also include updates provided by USDA's Economic Research Service (ERS) on projected imports. We conclude that the results of our assessment are robust to these updates. The changes to the assessment since the proposed rule improve the transparency and accuracy of the document, but they do not lead us to question or alter our conclusions that the likelihood of BSE establishment in the United States and the impacts of any additional cases resulting from the changes outlined in the proposed rule, will be negligible.

Updates following peer review and availability of more recent data

In compliance with OMB guidelines (OMB 2004), USDA APHIS arranged for peer review of the risk assessment published in support of the proposed rule. The risk assessment was peer reviewed by four experts in the fields of BSE, modeling, quantitative risk assessment and its application to regulatory decision making, and international health standards. The charge to reviewers, peer review report (RTI 2007) and our response are available at http://www.aphis.usda.gov/peer_review/peer_review_agenda.shtml. The reviewers found that the methods used in the risk assessment were scientifically rigorous "in terms of using existing literature and models appropriately and making sound assumptions" and adhered to international risk assessment standards. The reviewers also agreed with the conclusion that the risk of establishment of BSE in the U.S. cattle population is negligible and noted that several assumptions in the risk assessment actually over-estimate the risk, reinforcing the overall finding that the BSE risk is negligible.

In addition to being supportive of the methods, evidence, and conclusions presented by APHIS in the risk assessment, the reviewers made several suggestions for the document's improvement. In this revised version of the risk assessment, we have incorporated clarifications and updates in consideration of these comments. While we expect that the changes improve the transparency and accuracy of the document, they do not question or alter our original conclusions that the risk of BSE establishment in the United States resulting from the changes outlined in the proposed rule is negligible.

One peer review suggestion was to revise the risk estimates in light of more recent BSE cases in Canada. Because the potential impact on the risk estimates due to changes in BSE surveillance data is determined through changes in prevalence (which can influence our expectations of release and hence exposure), we first determine if these additional cases challenge our previous prevalence estimates. In order to more thoroughly determine if the risk estimates are robust to updates in other data relevant to estimates of release, exposure and risk, we also consider USDA ERS' most recent import projections. Because these updates do not significantly change either the prevalence estimate or the import projections, we have elected not to rerun the Harvard model used to inform the exposure assessment. To allow maximum transparency, without introducing confusion with the original inputs to that model, we include discussion of this more current information in this "Updates" section.

Consideration of prevalence estimate in light of additional cases

Attachment 1 of APHIS' risk assessment published in support of the proposed rule (APHIS 2006b) estimated Canadian BSE prevalence based on a 7-year surveillance period through August 15, 2006. This surveillance period included the detection of nine BSE cases of Canadian origin reported through August 2006. Based on surveillance conducted from August 16, 2006, through April 2007, Canada detected one BSE case born in 2000 and another born in 2001 (CFIA 2007). The BSE prevalence estimation methods used by APHIS (2006b) require detailed data to stratify tested cattle by age and

cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) that are unavailable for the more recent surveillance period. However, we can determine the robustness of the previous Canadian BSE prevalence estimates by comparing them to those obtained simply by adding the two additional cases without changing the BSE surveillance points accumulated by Canada during the 7-year surveillance period through August 15, 2006 (APHIS 2006b, Table 4). This approach results in a revised table of BSurvE points and BSE cases by birth year cohort that reflects a total of 11 BSE cases of Canadian origin reported through April 2007 (Table i, below).

Table i. BSurvE points and BSE cases by birth year cohort

Birth year	BSurvE Points	BSE Cases
1991	24,737	1
1992	35,814	0
1993	61,914	0
1994	115,950	0
1995	183,528	0
1996	225,473	2
1997	217,155	2
1998	173,111	1
1999	142,290	0
2000	150,111	3
2001	128,565	1
2002	59,090	1
2003	13,894	0
2004	558	0
2005	2,170	0

Using the same methods described in APHIS (2006b), we obtain updated Canadian BSE prevalence estimates:

BSurvE Prevalence B: 90 percent confidence interval = 3.0 to 8.0 per million
Bayesian Birth Cohort (BBC, WinBUGS): 90 percent confidence interval = 0.47 to 1.2 per million

Because the updated confidence intervals contain the previous expected value estimates of 0.68 per million (BBC) and 3.9 per million (BSurvE Prevalence B) (APHIS 2006b), we do not find it necessary to change the prevalence estimates used in the October 2006 risk assessment (APHIS 2006a).

Also, as stated by the peer reviewers, assuming constant prevalence (at either of the considered levels) over 20 years is in itself a very pessimistic assumption. By virtue of this assumption, we are likely overestimating the number of cases in Canada that are incorporated into the quantitative exposure model used to inform the exposure assessment. Thus, the conclusions of our analysis are robust to the potential identification of additional cases during surveillance.

Updates to the live bovine import projections

In order to more thoroughly evaluate the potential impacts on our risk estimates of more recent data, as explained above, we consider updates by USDA ERS in the projected bovine imports by age and use class. These projections are also used by APHIS in the regulatory impact analysis prepared for publication with the final rule; therefore including them here ensures that the analyses consider the same underlying data. Additional details are provided in Appendix 1 of the Regulatory Impact Analysis and Final Regulatory Flexibility Analysis (APHIS 2007). In this section, we present a discussion of the factors that have altered ERS' projections from those provided for the original analyses and why these changes do not challenge our original conclusions regarding likelihood of release of BSE, nor, therefore, regarding exposure from, or resulting consequences of these imports.

Updated projected cattle imports for 2007

Since the import projections were developed for the proposed rule, two contributing factors have changed based on more recent data and information. The first factor is the anticipated growth of bio-fuel production in the United States and elsewhere. This novel use of grain affects the livestock sector by raising grain prices and, hence, feeding costs. The U.S. cattle herd is entering an expansionary phase of the cattle cycle, but higher expected grain prices have dampened the anticipated herd expansion as noted in the 2007 baseline projections.

The second factor is the need for age verification, which specifically impacts the cull cattle import projections. Information received during the comment period indicated that the overall number of cull cattle that would qualify for importation would be markedly reduced because of the limited number of such animals that can have their ages verified in a satisfactory manner. The USDA Foreign Agricultural Service (FAS) office in Canada estimates that only 20-25 percent of Canadian cattle can have their ages verified appropriately. The effects of the March 1, 1999, birth date restriction and the age-verification restriction are dramatic. Of the cull cattle which we otherwise project might be imported, only about one-fourth are expected to be eligible in 2008 and only about one-half by 2012. The updated import projections reflect this decrease in the projected imports of cull cattle.

In addition to incorporating the above two factors, the updated import projections differ from the 2006 projections in that they reflect a return to the previous close relationship between the U.S. and Canadian cattle inventories. Year-to-year percentage changes in the Canadian inventory are expected to slightly exceed those projected for the U.S. herd. The percentage changes are obtained by adding a "Canadian increment" of 0.3 percent to the yearly percentage changes in the U.S. cattle inventory projections taken from the USDA Baseline. The beginning Canadian inventory in 2008 is a revised number taken from the March 2007 FAS-USDA semi-annual review of country-level production, supply, and distribution of livestock products.

The Canadian slaughter cattle export projections are based on 2007 exports (from USDA's *World Agricultural Supply and Demand Estimates*), adjusted by the projected change in Canada's cattle inventory. Slaughter cattle import volumes are further adjusted downward to reflect greater competition from Canadian packers for slaughter animals of all types, as U.S. imports of cull slaughter cattle resume. In other words, the slaughter of an additional quantity of fed cattle is expected to occur in Canada, in place of a portion of the cull cattle exported to the United States with the rule, to meet the throughput demand of Canadian slaughter plants. Feeder cattle markets should be affected only indirectly by the rule, to the extent that the rule affects the overall size of the Canadian herd.

Table ii. Average import percentages of cattle from Canada as a result of regulatory changes 2008-2027 based on 2007 projections

	Percentages	
	Sub-group	Overall
Slaughter cattle		75.3
Steers/heifers*	51.8	
Cows	16.6	
Bulls and stags	3.1	
Calves*	4.0	
Stockers/feeders*		20.2
Breeding cattle		4.4
Dairy heifers/cows*	3.8	
Beef heifers/cows*	0.4	
Bulls*	0.2	
Total		100

Table iii. 2007 updates for projected imports of various cattle use types for years 1 through 20[2]

				Projected cattle imports to US from Canada, by category -- 1,000 head										
	Canadian	Inventory		U.S.	SLAUGHTER CATTLE					BREEDING CATTLE				Stocker/
	Inventory	as pct of	Pct		Steers &	Cows	Bulls	Vealers /	Sub-	Dairy cows	Beef cows	Bulls	Sub-	feeders
YEAR	,000 hd.	last year	exported	,000 hd.	heifers		& stags	Light calves	total	/ heifers	/ heifers		total[3]	(male+fem)
1	13,860	96.8	8.06	1,117	686	63	12	49	810	48	5	3	55	252
2	13,861	100.0	8.08	1,120	685	67	12	49	813	48	5	3	55	252
3	13,855	100.0	8.09	1,121	685	68	13	49	814	47	5	3	55	252
4	13,871	100.1	8.38	1,162	672	113	21	49	855	48	5	3	55	252
5	13,951	100.6	8.52	1,189	669	136	25	49	880	48	5	3	56	253
6	14,166	101.5	8.61	1,219	675	152	28	50	906	49	5	3	56	257
7	14,403	101.7	8.70	1,252	682	169	31	51	933	49	5	3	57	262
8	14,608	101.4	8.83	1,291	685	194	36	52	967	50	5	3	58	265
9	14,770	101.1	8.98	1,326	686	220	41	52	999	51	5	3	59	268
10	14,367	97.3	9.11	1,309	661	235	44	51	991	49	5	3	57	261
11	14,216	98.9	9.22	1,311	649	250	47	50	996	49	5	3	57	258
12	14,544	102.3	9.30	1,353	660	270	50	52	1,031	50	5	3	58	264
13	14,619	100.5	9.35	1,367	661	279	52	52	1,044	50	5	3	58	266
14	14,770	101.0	9.38	1,386	666	287	53	52	1,059	51	5	3	59	268
15	14,997	101.5	9.40	1,410	675	295	55	53	1,078	51	5	3	60	272
16	15,325	102.2	9.42	1,444	689	304	57	54	1,104	53	5	3	61	278
17	15,476	101.0	9.42	1,459	696	308	57	55	1,116	53	5	3	62	281
18	15,577	100.7	9.43	1,468	700	310	58	55	1,124	53	5	3	62	283
19	15,779	101.3	9.43	1,488	709	315	59	56	1,138	54	5	3	63	287
20	16,132	102.2	9.43	1,521	725	322	60	57	1,164	55	5	3	64	293

[2] Because of the later time frame for the revision, year 1 is now 2008.
[3] In this table and others we represent large values with few significant digits, leading to occasional rounding error.

Updated projected bison imports for 2007

The following information was provided by USDA ERS as part of their updated 2007 import projections for cattle and bison.

As indicated in the original risk assessment, most bison imports (80 percent) are for slaughter, 10 percent are for breeding, and 10 percent are imported as feeding animals. However, the number of bison imported has been revised to reflect the higher volume of imports observed in 2006, when imports of bison from Canada jumped significantly, reaching 13,255 head. Records on bison imports first appear in U.S. official trade data in 1996, and average bison imports between then and 2005 were 2,622 head per year, excluding 2004 when the import ban was in effect throughout the year. The maximum annual value during this period was 4,490 head in 1999 and the minimum value was 991 in 2003, when the border was open for only the first 5 months.

The projected volume of bison imports is therefore assumed to be 12,000 head per year to more closely reflect the 2006 experience. This level is assumed to be constant over the next 20 years. The percentages of animals assigned to each use (breeding, slaughter, and feeding) were maintained at the levels indicated above and in Table iv.

Table iv. Updated projected bison imports to United States from Canada by usage category

YEAR	Canadian Bison Exports to United States	Slaughter	Breeding	Stocker/Feeders
1-20	12,000	9,600	1,200	1200

Source: ERS Market and Trade Economics Division, Animal Products Branch.

Imports of BSE-infected live bovines

Average annual imports of BSE-infected cattle

Projected imports are a key component of the likelihood of release of infectivity. On pages 11-12 of the Updates section of the assessment we demonstrate that adding the two additional BSE cases detected in 2007 does not lead us to change our prevalence estimates for Canada. More recent import projections described above indicate that the proportional and absolute numbers of older cull cattle imported will be far less than originally estimated. This drop stems primarily from the expectation that only 20 to 25 percent of cull cattle will be age-verifiable at the start of the import period (2008), going up to 50 percent by 2012. Although the total number of imports across all age classes is not projected to be lower than our initial projections, the number of cull cattle is expected to be lower (Tables iii and v). The difference is compensated for by a significant rise in the numbers of young slaughter and feeder cattle. No significant change in the number of breeding cattle is expected. Thus, there is no reason to expect these changes to the import projections to impact the findings of our release assessment.

Table v. Updated projected percentages, total (number), and infected cattle imports by usage type from Canada averaged over the 20 years of the analysis. The two prevalence estimates reflect the two methods used in Section III.A.

	Percentages		Average Number Imported	Average Annual Infected Imports by Class	
	Sub-group	Overall		Prevalence= $6.8*10^{-7}$	Prevalence= $3.9*10^{-6}$
Slaughter cattle		75.4	991,088	0.67	3.87
Steers/heifers	51.8		680,848	0.46	2.66
Cows	16.6		217,763	0.15	0.85
Bulls and stags	3.1		40,493	0.03	0.16
Calves	4.0		51,983	0.04	0.20
Stockers/feeders		20.2	266,219	0.18	1.04
Breeding cattle		4.4	58,338	0.04	0.23
Dairy heifers/cows	3.8		50,234	0.03	0.20
Beef heifers/cows	0.4		4,975	0.00	0.02
Bulls	0.2		3,129	0.00	0.01
Total	100	100	1,315,645	0.89	5.13

The updated projections corresponding to the less likely quantitative scenarios used in the exposure model are represented in Table v, above. This table provides the average annual imports by class and Canadian BSE prevalence estimate over the 20 years of the analysis. When compared to Table 7 in Section III.D.1., which presents the original average release expected for 2007 (a year of relatively high imports under the original projection model), the average release under the updated projections is slightly lower. This average release incorporates the risk-inflating assumption of no drop in BSE prevalence in Canada over the 20 year period of the analysis. Even under this assumption, we do not anticipate any significant increase in the quantitative release estimates.

Imports of BSE-infected bison

Based on the 2007 import projections (Table iv), we expect 12,000 bison to be imported annually for the next 20 years. Using our original prevalence estimates, these numbers correspond to an expected value of 0.047 infected animals annually or one infected animal in over 21 years when assuming no drop in prevalence due to the feed ban, now or in the future (i.e., using the BSurvE estimate). When incorporating the evidence from the UK on the impact of a feed ban (i.e., using the expected value of the BBC prevalence estimate), this proportion drops to 0.008 animals annually, or one in 123 years.

Conclusion: Impacts of data updates on risk estimates associated with imports of live bovines

We have demonstrated that our release estimates for live bovines are not sensitive to updates in the Canadian BSE surveillance data or the import projections for cattle and bison. The likelihood of BSE release remains extremely low and therefore there was no need to rerun the exposure model with different release estimates. Thus, we have not changed our overall conclusions that the likelihood of BSE establishment and the impacts of additional cases as a result of importing live bovines, blood and blood products, or small intestines from Canada, are negligible.

I. Introduction

The Bovine Spongiform Encephalopathy Minimal Risk Regions (BSE MRR) rule

The BSE MRR rule (APHIS 2005) established the criteria for a BSE minimal risk region, determined that Canada met those criteria, and specified the commodities permitted import under the regulation. We are not proposing to amend either the criteria for a BSE minimal risk region, or the designation of Canada as meeting those criteria in this rule. We are, however, proposing to amend the commodities permitted for import under the MRR designation.

The BSE MRR regulation in Title 9 of the *Code of Federal Regulations* (9CFR), Part 94.0, defines a BSE minimal-risk region as a region that:

1. Maintains and, in the case of regions where BSE was detected, had in place prior to the detection of BSE in an indigenous ruminant, risk mitigation measures adequate to prevent widespread exposure and/or establishment of the disease. Such measures include the following:
   - Restrictions on the importation of animals sufficient to minimize the possibility of infected ruminants being imported into the region, and on the importation of animal products and animal feed containing ruminant protein sufficient to minimize the possibility of ruminants in the region being exposed to BSE;
   - Surveillance for BSE at levels that meet or exceed recommendations of the World Organization for Animal Health (Office International des Epizooties) for surveillance for BSE; and
   - A ruminant-to-ruminant feed ban that is in place and is effectively enforced.
2. In regions where BSE was detected, conducted an epidemiological investigation following detection of BSE sufficient to confirm the adequacy of measures to prevent the further introduction or spread of BSE, and continues to take such measures.
3. In regions where BSE was detected, took additional risk mitigation measures, as necessary, following the BSE outbreak based on risk analysis of the outbreak, and continues to take such measures.

The criteria for minimal risk regions ensure that such regions have taken appropriate control measures to maintain a low prevalence of BSE and conduct surveillance in accordance with international guidelines to monitor the presence of disease. Existing regulations allow the importation, under certain conditions, of live ruminants and certain ruminant products and byproducts. Previous risk assessments concluded that live bovines could be safely imported as long as they were slaughtered before they were 30 months of age. To ensure slaughter by this age limit, regulations were established concerning identification, controlled movements, and monitoring. These assessments also concluded that bovine meat and meat products could also be imported under certain conditions.

Both the United States and Canada have conducted extensive surveillance programs since the middle of 2004. Since January 4, 2005, when the final rule recognizing Canada as a minimal risk region was published, seven cases of BSE have been identified in Canada.

In the United States, two indigenous cases of BSE have been identified - one in July 2005 and one in March 2006. The additional information obtained from these surveillance efforts and additional epidemiological analysis of all of the BSE cases support the substantive analysis outlined in this document. This analysis used these sources of epidemiological information, along with published literature to evaluate the BSE risk (as described below) of allowing the import into the United States from Canada of certain additional live bovines, certain bovine blood and blood products, and bovine intestines, other than the distal ileum.

Scope

The primary purpose of this analysis is to determine the BSE risk to the United States associated with the commodities in the revised regulation. Specifically, the BSE risk evaluated in this assessment is the expected impact of importing from Canada certain live bovines, blood and blood products and small intestines excluding distal ileum. These impacts include the potential for establishment of BSE in the Unites States and the potential consequences of any additional cases that might occur even without establishment. Therefore, the risk we evaluate includes both the likelihood of BSE establishment and the impacts of cases that might occur even without establishment. The risk is evaluated qualitatively for all commodities and also quantitatively for more risk-inflating live animal import scenarios. For the latter, the likelihood of establishment is measured by the disease reproductive rate (R_0) and the number of animals in the United States infected with BSE after 20 years of simulated analysis. Of the infected animals, those that we assumed that might have economic impacts were only the animals expected to live long enough to display clinical signs, as these are the most likely to be detectable with current testing methods.

USDA APHIS' regulatory authority under the Animal Health Protection Act covers factors impacting the health of livestock. Therefore, the scope of this risk assessment is limited to animal (specifically, bovine livestock) health pathways and consequences. Other potential impacts on aspects of the "human environment,"[4] including public health, are addressed to comply with the National Environmental Protection Act (NEPA) in the accompanying environmental assessment (APHIS 2006).

To facilitate the quantitative analysis of the likelihood of release and spread of BSE via imports of live bovines, we use a screening approach which includes all bovines that would be allowed entry under the regulation. Thus, the analysis is not incremental in that we include animals that are already allowed entry under current regulations. We recognize that by including in the analysis animals that are already allowed entry (for slaughter by 30 months of age) we are increasing the estimated number of imported infected animals beyond that which may result from these regulatory changes alone. If the risk associated with the entire group analyzed is acceptable, then no further analysis is necessary. However, the analysis is not cumulative in that we do not consider the level of indigenous infectivity that may currently be present in the U.S. cattle population.

[4]Under NEPA regulations, "human environment" is interpreted to include the natural and physical environment and the relationship of people with that environment.

Format

The format of this risk assessment follows OIE guidelines. The risk assessment proper is preceded by a Hazard Identification section in which we specify the pest or disease of livestock for which we are assessing the risk. In this case, we are restricting the assessment to BSE that may be released as a result of the importation of live animals and certain bovine-derived products from Canada, a BSE minimal risk region. The risk assessment itself includes the four sections specified by the OIE *Terrestrial Animal Health Code* Section 1.3 Risk Analysis (OIE 2006b). The Release Assessment evaluates the likelihood that animals or products permitted entry from Canada will introduce the BSE agent into the United States. In order to make that evaluation we consider the probability of introducing any BSE infectivity (e.g., by importing one or more infected cattle over time), frequency (e.g., the number of imported infected animals per year), and magnitude (e.g., both the number of infected animals over the period of analysis and the amount of infectivity these animals are likely to carry). The Exposure Assessment evaluates the likelihood of exposure, establishment and spread of the BSE agent in the United States given that it has been released. The Consequence Assessment addresses the impacts expected if, as a result of the amended rule, additional BSE cases were to occur in the United States. Finally, in the Risk Estimation, we combine the findings of the release, exposure, and consequence assessments to express the overall risk of BSE (the likelihood of establishment and the impacts of cases that might occur even without establishment) associated with the regulatory changes regarding bovine imports from the minimal risk region (Canada).

This risk assessment, according to the approach as it is applied across a variety of disciplines, breaks down the possible pathways for the undesired outcome (in this case, the establishment of BSE in the U.S. cattle population) into a series of steps, or nodes. Some of the nodes are in series; in order for one to occur, a previous one must have occurred. The likelihood of occurrence of a series of sequential steps is the product of the likelihood of each of the individual steps occurring. This multiplicative effect takes place whether or not an analysis is performed quantitatively or qualitatively. Some steps in the risk pathways can occur without the occurrence of other steps. These are said to function in parallel, and are therefore, additive in their impact on the likelihood of the undesired outcome. Because the impact of any specific step depends on its relationship to other steps, its importance to the overall likelihood of the undesired outcome cannot be understood in isolation from the rest of the pathway. Therefore, in risk assessment, although we analyze the likelihood of each individual step in the process, we interpret its significance in the context of the entire process. For example, in this assessment, we present evidence for the likelihood of release from Canada to the United States. However, to understand the impact of the amount of infectivity released, it must be interpreted together with the outcome of the Exposure and Consequence Assessments.

History of BSE in Canada

As of October 27, 2006, a total of nine BSE cases of Canadian origin had been confirmed. This number includes one case of Canadian origin that was identified in the United States in December 2003. The first native Canadian case was identified in May

2003, and was followed that year by the December case identified in the United States. In response to the finding of BSE in Canadian cattle, the Canadian Food Inspection Agency (CFIA) intensified their surveillance efforts and had identified seven additional cases through October 27, 2006. Two additional cases were identified after the release of the proposed rule (i.e., through August 2007).[5]

Epidemiological investigations have shown that BSE initially entered Canada in the 1980s via an infected animal or animals that were imported from the UK. It is likely that rendered meat and bone meal (MBM) produced from these animals were included in cattle feed, a practice that was permitted at the time, and this practice led to the development of additional cases of BSE in Canadian-born cattle (USDA 2005a).

Canada imported 182 cattle from the UK between 1982 and 1990. Following the detection of an imported case of BSE in 1993, all remaining UK imports were slaughtered and incinerated, or returned to the country of origin (USDA 2005a). The BSE risk status of the Canadian birth cohorts was assessed based on demographic factors, age, and the BSE status of their UK herd of origin. The assessment indicated that of the 52 animals shipped to the Province of Alberta, three were from cohorts of UK cattle with BSE. One of these was the animal that tested positive for BSE in 1993; the resulting investigation determined that the other two had already died and most likely entered the feed processing system prior to the detection of the first case. Therefore, a likely scenario is that MBM containing specified risk materials (SRM) from one or more infected animals contaminated the Canadian feed system and was recycled during the early 1990s. Considering the average incubation period for BSE, CFIA believes that Canada's BSE cases represent the second generation (or amplification cycle) in that country (CFIA 2006).

Investigations conducted in 2003 and 2004, following the diagnosis of an indigenous case of BSE, revealed geographical proximity among the origins of all the Canadian BSE cases and the destinations of cattle imported from the UK (USDA 2005a). The destinations of the UK imports and origin of the Canadian BSE cases were clustered in a relatively small geographic area in central Alberta and western Saskatchewan. Further investigations carried out by CFIA revealed that renderers, feed mills and farmers across Canada are grouped by geographic and economic forces into "clusters" (CFIA 2006). Since the distribution of MBM in Canada is generally localized, the disease was most likely recycled primarily within a geographic feed zone unless infected cattle and/or contaminated MBM were moved to other areas. Specifically, one of the regional rendering facilities in Alberta processing high risk BSE animals (downers and dead stock) used a particular low temperature "vacuum" process that does not reduce BSE infectivity (zero log reduction). This practice most likely allowed the recycling through the feed chain of infectious materials from high risk animals and further contamination of cattle feed prior to implementation of the feed ban. CFIA concluded that all indigenous Canadian cases detected to date have been associated with the cluster where this

[5] Since they occurred after publication of the original assessment, these two cases were not included in the associated quantitative analysis. However, as discussed in the "Updates" section of this assessment, the results of the assessment are not sensitive to the addition of these cases.

particular low temperature vacuum rendering system was used (USDA 2005a). After 1997, in compliance with the feed ban, prohibited ruminant material produced by the low temperature vacuum rendering system was not used in ruminant feed, although this ruminant derived material was still available for feeding to non-ruminants. To deter farmers and ranchers from accidentally or intentionally feeding prohibited material to ruminants, products containing ruminant derived material had to be labeled with the caution statement, "Do not feed to cattle, sheep, deer, or other ruminants." Therefore, the implementation of the feed ban in 1997 reduced, if not eliminated, the recycling of BSE infectivity and greatly decreased the likelihood that cattle born after implementation of the feed ban would be exposed to the BSE agent.

With one exception, epidemiological investigations completed by October 2006 indicate that all indigenous Canadian BSE cases were born and spent their first 12 months of life within the cluster area, or were exposed to feed from within the cluster area (CFIA 2006, CFIA 2006b). The detection of additional cases within either this recognized cluster or further clusters that might be defined in the future cannot be ruled out. Such detections do not necessarily negate the assumptions and findings of this assessment. The one case detected to date that was not associated with the recognized cluster area was an approximately 16 year old cow in Manitoba, which was determined to have a different phenotype than the other cases. The CFIA investigation reported that this case had a phenotype consistent with a less prevalent strain of BSE previously reported in Europe and the United States (CFIA 2006b).

The recognition of clusters in which BSE cases were likely exposed does not automatically imply that the originating region will have a higher prevalence of BSE than other regions. We expect that movement of animals between the time of exposure and subsequent slaughter, development of clinical symptoms, or export minimizes the potential significance of such initial clustering on the likelihood of infected animals will be found in a particular region. Moreover, even if such differences existed, the very low numbers of reported BSE cases prevent any statistical distinction among provinces.

II. Hazard Identification

The agent of interest in this analysis causes bovine spongiform encephalopathy (BSE). The scenarios of interest are the importation of live bovines born after the date of an effectively enforced feed ban, and the importation of certain commodities derived from cattle (blood and blood products and small intestines other than distal ileum) into the United States from Canada.

BSE is not a contagious disease, and therefore is not spread through casual contact between animals. Instead, evidence indicates that transmission requires that cattle ingest feed that has been contaminated with tissue from an infected animal. Several steps must take place for this to happen – an infected animal, carrying significant amounts of the infectious agent, must die or be slaughtered; tissues from that animal that contain the infectious agent must be sent to a rendering facility; the infectivity present in these tissues

must survive inactivation in the rendering process; the resulting protein must be incorporated into feed and this feed must be fed to at least one bovine at a level adequate to result in infection given that animal's age-specific susceptibility. As will be discussed later in this document, there are several barriers at different steps in this process that decrease the possibility of infection as outlined.

BSE is a progressive neurological disorder of cattle that research suggests is caused by a pathogenic form of a normally occurring protein known as a prion (PrP) (Bolton, et al. 1982; Prusiner 1994). BSE belongs to a family of diseases known as transmissible spongiform encephalopathies (TSEs). In addition to BSE, TSEs include, among others, scrapie in sheep and goats, chronic wasting disease in deer and elk, transmissible mink encephalopathy, and Creutzfeldt-Jakob disease (CJD) in humans.

The pathogenic form of the prion protein (PrP^{Sc}) is both less soluble and more resistant to degradation than the normal form (Taylor 2000; Taylor, et al. 1995). The PrP^{Sc} is extremely resistant to heat and to normal sterilization processes, making it difficult to inactivate with standard methods used to process human food and animal feed. Although rendering and other processes can partially inactivate PrP^{Sc}, the risk mitigation strategies (for meat and meat products) rely mainly on the elimination of tissues and organs known to carry infectivity.

The agent does not evoke a traditional immune response or inflammatory reaction (Khalili-Shirazi, et al. 2005), thus reliable ante-mortem diagnostic tests based on host reaction are not available. Definitive diagnosis requires post-mortem microscopic examination of brain tissue or detection of PrP^{Sc} in tissue samples.

In the past few years, cases of BSE have been identified throughout the world in which various biological features differ, such as molecular characteristics of the abnormal prion protein or histopathological lesions (Béringue, et al. 2006; Casalone, et al. 2004; De Bosschere, et al. 2004; Buschmann, et al. 2006; Buschmann, et al. 2006a; Lloyd, et al. 2004; Yamakawa, et al. 2003). These cases have generally been referred to as "atypical BSE", although the literature describes several different forms of unusual cases. To date, however, the understanding of the risk of transmission of BSE (and/or the SRM definition) remains unaltered, even when incorporating these recently identified unusual or so-called "atypical" BSE cases (OIE 2003).

The following paragraphs detail the relevant characteristics of BSE overall, including transmission, incubation period, tissue distribution, and infectivity of the BSE agent in cattle, its most common host.

II.A. *Transmission*

The primary source of BSE infection is commercial feed contaminated with the infectious agent. Scientific evidence (Wilesmith, et al. 1988; 1991; 1992) shows that feed contamination results from the incorporation of ingredients that contain ruminant protein derived from infected animals. Standard rendering processes do not completely

inactivate the BSE agent. Therefore, rendered protein such as meat-and-bone meal (MBM) derived from infected animals may contain the infectious agent. Bans prohibiting incorporation of mammalian or ruminant protein into ruminant feed are imposed to mitigate the risk of BSE transmission.

Oral ingestion of feed contaminated with the abnormal BSE prion protein is the only documented route of field transmission of BSE (Prince, et al. 2003; Wilesmith, et al. 1988; 1991; 1992). However, results of a UK cohort study indicated that offspring of BSE-affected dams were at a higher risk of also developing clinical BSE, suggesting the possibility of maternal (vertical) transmission (Wilesmith, et al. 1997). These results are consistent with a rate of maternal risk enhancement of approximately 10 percent in the offspring born within 12 months of the dams' onset of clinical signs of BSE. Since the initial cohort study, modeling studies based on the epidemic data from the UK have indicated that the cumulative maternal risk is only 1 percent in calves born in the last 6 months of incubation of the disease in its dam (Donnelly, et al. 2002). More recent work on cases born after the 1996 feed ban fails to demonstrate evidence of maternal transmission (Hill 2005). Thus, although maternal transmission may be possible, more recent epidemiologic evidence suggests that maternal transmission of BSE is unlikely to occur at any appreciable level, if at all.

Epidemiological studies and mathematical modeling have supported the view that most cases were likely exposed as calves (Wilesmith, et al. 1988) with most chances of becoming infected up to or around the first year of life (Wilesmith, et al. 1992 and 1992a; Ferguson, et al. 1997; De Koeijer, et al. 2004; Arnold and Wilesmith 2004). These findings suggest that susceptibility in cattle declines with age, and, therefore, young animals are most susceptible. One mathematical model assumes that animals consuming BSE infectivity that are older than four months of age are less susceptible than younger animals. Specifically, this simulation assumes that susceptibility declines exponentially after the age of 4 months leveling off at 10 percent of the peak value (De Koeijer, et al. 2004).

A study from Great Britain published the same year (Arnold and Wilesmith 2004) used unpublished data on the feeding of proprietary concentrates to replacement dairy cattle and BSE-epidemic data to back-calculate the likely age of infection. This study found that dairy cattle were at greatest risk in their first six months. Although this result likely confounds susceptibility with exposure, because of age-dependent patterns of nutritional supplementation, they are effectively linked.

Experience in the UK demonstrates that implementation of a ruminant-to-ruminant feed ban exerts downward pressure on the prevalence of BSE (Figure 1). Animal feed restrictions began in the UK in July 1988, when the use of ruminant MBM in ruminant animal feed was banned. In September 1990, the use of Specified Bovine Offals (SBO) was banned for use in any animal feed in the UK. This ban prohibited the use in any animal feed of bovine tissues with the highest potential concentration of infectivity. In 1994, the use of mammalian protein – not just ruminant protein – was banned from ruminant feed. In 1996, feeding of any farmed livestock, including fish and horses, with

mammalian meat and bone meal (mammalian MBM) was completely banned. As a result of these bans to reduce the recycling of infectivity, the annual incidence of BSE fell by 99.4 percent from 36,680 in 1992 to 203 in 2005 (DEFRA 2006b).[6]

When the UK epidemic is plotted by year of birth, the impact of the feed ban is striking. Although the data that are presented in the following figure and table represent the specific situation in the UK[7] during the years identified in the graph, we expect similar effects (i.e., downward pressure on the prevalence of BSE) in any country with BSE that implements a comparable feed ban.

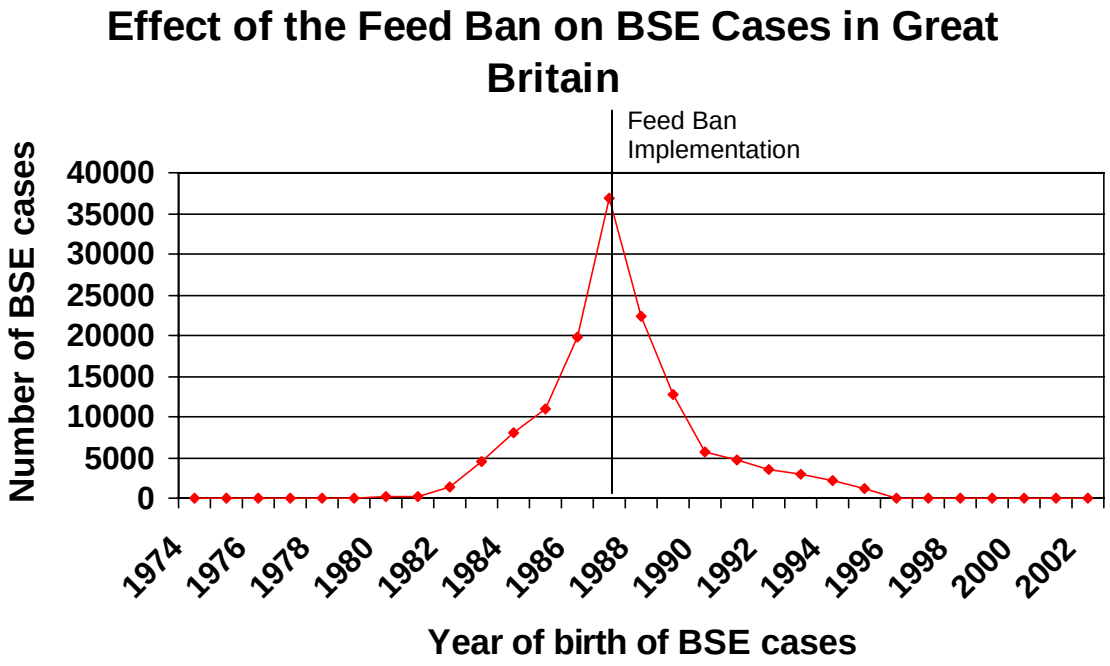

Figure 1. Confirmed cases in cattle born in Great Britain after feed ban implementation. **Note:** The first feed ban was implemented in the summer of 1988 (before fall calving). Source of data represented in figure and in Table 1: DEFRA 2006a.

The raw data that provided the basis for Figure 1 are reproduced in Table 1.

[6] The OIE Terrestrial Animal Health Code (Chapter 1.1.1., Article 1.1.1.1) defines incidence as "the number of new cases or outbreaks of a disease that occur in a population at risk in a particular geographical area within a defined time interval" (OIE 2007).

[7] The data made available by DEFRA on its website are for Great Britain, which does not include Northern Ireland. These data also exclude the Channel Islands and Isle of Man. Records published elsewhere indicate that the vast majority of BSE cases in the UK have been detected in Great Britain (OIE 2006). therefore, epidemiologic patterns noted in Great Britain represent the overall UK experience.

Table 1. Confirmed cases in Great Britain by year of birth, where known

Year	Cases	Year	Cases
1974	1	1989	12,748
1975	0	1990	5,747
1976	2	1991	4,779
1977	10	1992	3,531
1978	6	1993	2,997
1979	41	1994	2,179
1980	102	1995	1,099
1981	262	1996	67
1982	1,394	1997	45
1983	4,463	1998	37
1984	8,069	1999	23
1985	11,071	2000	5
1986	19,752	2001	5
1987	36,935	2002	1
1988	22,266	Unknown birth year	43,340
Total: 180,977			

Source: DEFRA 2006a.

Despite the dramatic evidence presented above, as of September 2006, 134 cases of BSE have been detected in UK animals born after the ban (BAB cases) reinforcement in 1996 (DEFRA 2006). Several analyses of the BAB cases suggest that the animals were likely to have been exposed to an exogenous feed source from continental Europe. For instance, based on the analysis of the first 16 cases (Wilesmith 2002) the author indicates that an exogenous (non-UK) feedborne source remains the most likely explanation, since trading of MBM was legally possible at ports of Continental Europe until the European-wide ban was introduced in January 2001. Significant amounts of ingredients for cattle feed were imported into the UK before 2001, and cross-contamination of feedstuffs and ingredients has occurred in a number of other BSE-affected countries. A recent report (Hill 2005) also indicates the association of BAB cases with imported feed until controls were strengthened throughout Europe.

II.B. *Incubation*

BSE has a long incubation period. Epidemiological data from the UK epidemic has demonstrated that, on average, cattle develop clinical signs four to six years after infection (Bradley 1991; Anderson, et al. 1996), though the incubation period can be longer or shorter than four to six years. In BSE, as in other TSEs, the total amount of infectivity in an animal increases throughout the incubation period reaching the highest load at the end, very close to the death of the animal. Infectivity is considered to increase exponentially after exposure, reaching 3 logs less than clinical cases by 70 percent of the incubation period, and 4.5 logs less than a clinical case at 50 percent of the incubation period (Comer and Huntly 2003).

The incubation period is thought to be inversely related to dose (e.g., low dose exposures have long incubation periods before clinical signs of disease become apparent). The Department for Environment Food and Rural Affairs (DEFRA) Veterinary Laboratories Agency (VLA) in the UK has carried out cattle oral challenge studies to determine the incubation period for a range of doses of BSE infected cattle brain (Anderson, et al. 1996). In the first attack rate experiments, groups of 10 calves were dosed orally with 3 X100g (100g on 3 successive days), 100g, 10g or 1g of brain tissue from clinically sick animals. All animals in the two higher dose categories (3x100 and 100gr, respectively), 7 out of 9 in the 10 g, and 7 out of 10 in the 1g trial groups developed clinical BSE. The incubation period (IP) for the 3X100g ranged between 33 and 42 months. The IP for the 100g was 33 to 61 months; for the 10g was 42 to 75 months; and for the 1g was 45 to 75 months. The remaining animals in this experiment were killed at 110 months after exposure and showed no pathological evidence of disease.

The second attack rate experiments extend these findings with lower doses. As of December 2005, at approximately 93 months post exposure, the authors have confirmed 3 of 5 animals as positive for BSE in the 1g trial group (IP 59-73 months), 6 out of 15 animals in the 0.1g group (IP 55-90 months), 1 out of 15 in the 0.01g group (IP 56 months), and 1 out of 15 in the 0.001g group (IP 68 months) (Matthews 2005 personal communication). The study is ongoing.

II.C. *Tissue distribution and infectivity*

Most of the information on the development and distribution of tissue infectivity in BSE infected cattle has been derived from experimental pathogenesis studies conducted in the UK (Wells, et al. 1994; 1998; 1999). In these studies, cattle were deliberately infected with BSE through oral exposure to the brain tissue of cattle with confirmed BSE. Subsets of the experimentally infected cattle were killed at regular intervals as the disease progressed. At each interval the tissues of the infected cattle were examined for histopathological changes consistent with BSE and for abnormal prion proteins. Also, at each interval, a mouse assay was done – i.e., tissues of the BSE infected cattle were injected intracerebrally and intraperitoneally into mice to identify those tissues of cattle containing infectivity.

The pathogenesis studies involved 30 animals, each of which received a single dose of 100g of infected brain at 4 months of age (Wells, et al. 1994; 1998; 1999). This dose is probably 10 -100 times greater than that associated with field exposure via feed (DEFRA 2005). The studies demonstrate that in cattle infected with BSE, the total amount of infectivity in the animal, as well as the distribution of infectivity in the animal's body, change over time (Wells, et al. 1994; 1998; 1999). The highest levels of infectivity were detected in the brain and spinal cord at the end stages of disease. Some cattle exhibited clinical signs of BSE as early as 35 months post oral exposure to the BSE agent. By 37 months post oral exposure, all five animals that were still alive demonstrated clinical evidence of BSE. Infectivity was found in cattle with clinical signs of BSE in the brain,

spinal cord, dorsal root ganglia (DRG),[8] trigeminal ganglia, and the distal ileum of the small intestine.

BSE infectivity was demonstrated in the brain, spinal cord, and DRG as early as 32 months post oral exposure to the BSE agent in some cattle (Wells, et al. 1994; 1998; 1999). Infectivity was demonstrated in these tissues three months before animals began to develop clinical signs of the disease. Infectivity was demonstrated in the distal ileum of cattle 6 to 18 months post oral exposure to the BSE agent and again at 38 months and 40 months post oral exposure. A more recent, similar study (Espinosa, et al. 2007), examined the infectivity of tissues from these same animals by intracerebral inoculation of highly sensitive transgenic mice overexpressing bovine PrP. This study's findings were similar to those of Wells, et al. described above. In addition, infectivity in the sciatic nerve was found at low levels only after 30 months from exposure. No detectable infectivity was found in the spleen, skeletal muscle, blood or urine of asymptomatic cattle.

As explained by DEFRA and by the European Commission's Scientific Steering Committee, a second phase of the pathogenesis studies, which uses a cattle bioassay as an endpoint, is being conducted to ensure that low levels of infectivity that may not have been detected in the first phase using the mouse bioassay are not missed (DEFRA 2005; EC SSC 2002b). This second phase of the study is still underway and is not expected to be completed for several more years. In the cattle bioassay, tissues from the same cattle orally exposed to BSE in the earlier pathogenesis studies, were injected directly into the brain of BSE-free cattle (DEFRA 2005). This method is considered to be several hundred-fold more sensitive in detecting BSE infectivity than the mouse bioassay (DEFRA 2005). Preliminary results from the cattle bioassay study demonstrate that, in addition to the materials that were found to contain infectivity when the mouse bioassay was used, the tonsils of calves 10 months post oral exposure to the BSE agent also contain infectivity. However, because only one of five animals injected with tonsil material from infected animals developed clinical BSE at 45 months post-inoculation, the level of infectivity in the tonsils appears to be very low.

In addition to these studies on experimentally infected cattle, distribution of tissue infectivity has also been studied in cattle exposed to BSE under field conditions. In these animals, at the end stages of the incubation period with demonstrated clinical signs, BSE infectivity has been confirmed by mouse bioassay only in the brain, spinal cord, and retina of the eye (EC SSC 2001).

In a recent study, mice, genetically engineered to be highly susceptible to BSE and to overexpress the bovine prion protein, were inoculated with tissues from an end-stage clinically affected BSE-infected cow (Buschmann and Groschup 2005). The sensitivity

[8]DRG are clusters of nerve cells attached to the spinal cord that are contained within the bones of the vertebral column. "DRG" as used in this document has the same meaning as the term "dorsal spinal nerve root ganglia." Trigeminal ganglia are clusters of nerve cells connected to the brain that lie close to the exterior of the skull.

of these mice to infection is significantly greater than other mice panels used in bio-assays, and the sensitivity is even greater than that of cattle by approximately 10-fold. This study demonstrated low levels of infectivity in the facial and sciatic nerves of the peripheral nervous system, when injected into these highly sensitive mice. A more recent study (Espinosa, et al. 2007) also using highly sensitive genetically engineered mice, but inoculated with tissues from asymptomatic cattle (described above), also detected low levels of infectivity in bovine sciatic nerve. While these are interesting findings that can help further characterize the pathogenesis of BSE, they cannot be easily extrapolated into the context of the risk presented by natural exposure pathways. The findings may be influenced by the overexpression of prion proteins in these genetically engineered mice. Any apparent levels of infectivity are low in these extremely sensitive mice and would be even lower in other species such as cattle. Moreover, the route of administration to the mice was both intraperitoneal and intracerebral, both of which are very efficient routes of infection as compared to oral consumption. Given all of these factors, we conclude that there is not sufficient information in this study to alter our understanding of the epidemiologically significant distribution of BSE infectivity in cattle.

The amount and distribution of infectivity in specific tissues from an infected cow have been estimated by Comer and Huntly (2003) in their evaluation of the available literature. Those summary results, presented in Table 2, describe distribution of infectivity in various tissues, *i.e.*, brain, spinal cord, DRG, trigeminal ganglia, tonsil, and distal ileum, of a BSE-infected cow. The table uses an estimated weight of each tissue in grams, the number of estimated cattle oral infectious dose-50 (ID_{50}) units[9] per gram, and the total number of cattle oral ID_{50} units attributed to each tissue to estimate a percentage of cattle oral ID_{50} units for each tissue.

Table 2. Infectivity in a clinical case of BSE (cattle oral ID_{50})

Tissue	**Weight**	**Infectivity**		**%**
	g/animal	ID_{50}/g	ID_{50}/animal	
Brain	500	50	25,000	60.2
Spinal cord	200	50	10,000	24.1
Dorsal root ganglia	30	50	1,500	3.6
Trigeminal ganglia	20	50	1,000	2.4
Tonsil	50	0.005	0.25	0.0
Distal ileum	800	5	4,000	9.6
TOTAL	**1,600**		**41,500**	

Source: Comer and Huntly 2003.

The table shows that 90 percent of the infectivity is associated with central and peripheral nervous system tissues, i.e., brain, spinal cord, DRG, and trigeminal ganglia. About 10 percent was associated with the distal ileum. Minimal infectivity was associated with tonsils in a clinically affected animal.

[9] BSE infectivity is expressed in terms of cattle oral infectious dose-50 units (ID_{50}). A cattle ID_{50} is defined as the amount of infectivity required to cause infection in 50 percent of an exposed cattle population (Cohen, et al. 2001).

III. Release Assessment

In this section of the risk assessment we assess the likelihood of each of the evaluated commodity groups to introduce BSE infectivity into the United States. In order to make that evaluation we consider the probability of introducing any BSE infectivity (e.g., by importing one or more infected cattle over time), frequency (e.g., the number of imported infected animals per year), and magnitude (e.g., both the number of infected animals over the period of analysis and the amount of infectivity these animals are likely to carry). To estimate the likelihood of release, we first evaluate the prevalence of BSE in Canada, using both quantitative and qualitative approaches. We then evaluate the specific risk reduction steps taken in Canada in association with each of the commodity groups: live bovines, blood and blood products, and small intestines other than the distal ileum. We also present numeric estimates of projected live bovine imports. We then combine the information presented in these sections to assess the release of BSE infectivity associated with each commodity group. All commodities are assessed qualitatively. In order to inform the quantitative exposure model described in Section IV.A., release of BSE via live bovines is assessed quantitatively, as well.

III.A. *Estimation of BSE Prevalence in Canada*

The purpose of this section is to estimate the prevalence of BSE in the adult cattle population of Canada. The detection of Canada's first native BSE case was confirmed on May 20, 2003. As of October 27, 2006, a total of nine BSE cases of Canadian origin had been confirmed in North America (CFIA 2006).[10] This total includes a case of BSE that was confirmed in Washington State on December 25, 2003. By comparison, the UK had detected 184,453 cases of BSE through September 2006 (OIE 2006).

Prevalence is defined as the proportion of infected animals in a population. Although the simplest approach to the estimation of prevalence is to calculate this proportion directly (e.g., # identified cases/# samples tested), the limitations of current testing methodology for BSE make this approach less meaningful. Like many transmissible spongiform encephalopathies (TSEs), BSE has an incubation period of several years. Current technology can only detect the disease very close to the end of the incubation period, up to 3 months before an animal begins to exhibit clinical signs. Therefore, infected but preclinical animals would not be detectable. The number of BSE cases detected through surveillance understates the disease prevalence because exposed animals may be incubating disease which would not always be detectable with current testing methodology. Furthermore, surveillance will miss a proportion of detectable (clinical or late incubation) cases. Therefore, statistical methods are applied to the available epidemiologic and surveillance data to estimate, with attendant uncertainty, the prevalence of BSE in Canada.

[10] As of August 26, 2007, Canada had detected two additional BSE cases that are not included in the quantitative analysis. We demonstrate in the Updates section (pp. 11-12) that the original prevalence estimates are not sensitive to these additional cases.

We have used two related, but distinct methods to estimate BSE prevalence in Canada (Attachment 1). Given its international prominence, we consider the European Union (EU) BSurvE model (Wilesmith, et al. 2004, 2005), recently developed for the purpose of estimating BSE prevalence in national herds. The BSurvE model is noteworthy for its sound epidemiologic structure, including stratifying cattle by age and cause of death and accounting for the relative likelihood of detecting BSE in various strata (EFSA 2004). The other prevalence estimation method used in this document, referred to as the Bayesian Birth Cohort (BBC) model, takes advantage of the BSurvE model structure to calculate BSE surveillance point values (random sample size equivalents) represented by targeted Canadian sampling of certain groups of cattle in which BSE cases are more likely to be detected. The BBC model adopts a Bayesian statistical framework to incorporate prior information about the decreased incidence of BSE observed in animals born after the initial ruminant-to-ruminant feed ban introduced in the UK in 1988. For the purposes of comparison and sensitivity analysis, the prevalence of BSE in Canada also is estimated using BSurvE.

The identical methodologies were used in the recently published and peer-reviewed U.S. BSE Prevalence document (APHIS CEAH 2006). The reviewers found that these models were statistically and epidemiologically sound.

III.A.1. BSurvE Model

We use as a basis for our prevalence estimates the "BSurvE" model developed in the EU (Wilesmith, et al. 2004). This model provides the benefit of combining surveillance data, population demographics, and knowledge of the disease pathogenesis with evidence of the relative likelihoods of infectivity in various sub-populations, to estimate BSE prevalence in the entire cattle population. Moreover, the prevalence estimate includes all infected cattle regardless of whether they are at a stage at which the disease is detectable.

Specifically, BSurvE stratifies cattle by age and cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) and accounts for the relative likelihood of detecting BSE in various strata. The model uses epidemiologic information of the disease that was accumulated during the UK and European outbreaks to predict parameters such as incubation period of BSE, probable length of an infected animal's life, and the dynamics of disease expression in infected animals. It combines this information with the age distribution of a country's national herd and its surveillance test data to achieve a set of point values for samples taken from cattle of different age and cause of death strata called surveillance streams. The points represented by an animal tested for BSE are based on the relative likelihood that the disease would be detected in an animal leaving the herd at a particular age and by a particular surveillance stream. Under this scheme, one point is equivalent to an animal randomly selected for testing from the national herd (Wilesmith, et al. 2004). We obtain the BSE surveillance points used as inputs to the BSurvE prevalence estimation model using BSurvE Version 06.03. The BSurvE spreadsheet model and documentation are available on the BSurvE Web site (www.bsurve.com). The Web site includes updates made to the BSurvE model,

documentation (Wilesmith, et al. 2004; 2005) that provides detailed description of the underlying functions of the model, and step by step user instructions.

III.A.2. Bayesian Birth Cohort Model (BBC): Inclusion of feed ban data

In order to halt the spread of BSE, all countries known to have had BSE cases have banned the feeding of ruminant protein to ruminants. Evidence gathered from countries, such as the United Kingdom, describes the decline in BSE cases following implementation of such feed bans (Schreuder and Wilesmith 1997). Therefore, Bayesian methods, which allow the combination of different types of information, can be used to incorporate this evidence with the surveillance data collected by a different country – in this case, Canada.

Because the provisions of the Canadian ruminant feed ban introduced in 1997 were comparable to or more restrictive than the UK feed ban in place from 1988 to 1994, we estimate the effect of a feed ban on BSE prevalence in Canada to be proportional to that observed in the UK during those years. The initial UK feed ban imposed in 1988 prohibited the inclusion of ruminant MBM in ruminant feed (DEFRA 2006c). In comparison, the Canadian feed ban prohibits the feeding of most mammalian proteins (with exceptions) to ruminants (CFIA 2002), and is therefore equivalent or more restrictive than the initial UK feed ban. In 1994, the UK requirements became more restrictive by prohibiting the use of any mammalian protein in ruminant feed. Additionally, U.S. veterinary epidemiologists reviewed records and conducted site visits to Canadian facilities to evaluate the efficacy of the Canadian ban and concluded that compliance with the feed ban was good, and that the feed ban was effectively enforced (USDA 2005). Although the degree to which the Canadian ban was able to reduce BSE transmission is difficult to measure directly, Cohen et al. (2001; 2003) concluded that the U.S. ruminant feed ban would rapidly decrease BSE prevalence following the ban even with a substantial initial infusion of infectivity. Since the U.S. and Canadian bans are similar to each other, it is reasonable to conclude that the findings of Cohen et al. (2001; 2003) would likewise apply to Canada.

The Bayesian Birth Cohort (BBC) model provides a more precise estimate of BSE prevalence in Canada[11] by combining the epidemiologic theory underlying the BSurvE model with information about the effect of the feed ban on prevalence, as well as with surveillance data. Like BSurvE, the BBC prevalence estimate includes all infected animals in the standing adult cattle population of Canada, whether or not they are detectable and uses BSurvE's methodology for obtaining BSE surveillance points, described above. As a starting point, the BBC model assumes that the BSE prevalence in cohorts born prior to the feed ban could range from 0 to 100 percent (i.e., the prior assumption was that prevalence is uniformly distributed between 0 and 100 percent). The prior assumption about prevalence is then modified with each iteration based on a

[11] In statistical terms, the BBC estimate is more precise than the BSurvE estimate in that the former has a smaller estimated confidence interval. Precision is distinct from accuracy. Different modeling assumptions would result in different prevalence estimates which may be more or less accurate predictors of future prevalence."

constant prevalence before the feed ban, a decline after the ban proportionate to the UK, and the accumulated surveillance data. The model uses the total number of BSurvE points from each of the 1993-2004 birth cohorts that were tested by Canadian surveillance over a 7-year period ending August 15, 2006, as evidence for estimating the current prevalence.[12] Prevalence of infected adult cattle alive on August 15, 2006, was estimated from the Bayesian model as the weighted sum of the individual birth cohorts' prevalence levels, where the weights are the proportion of infected animals born into each cohort that remain alive in August 2006.

The BBC model was implemented using two Bayesian analytical methods: Gibbs sampling and Sampling-Importance-Resampling (SIR). Gibbs Sampling is a Monte Carlo Markov Chain (MCMC) statistical method (Vose 2000). MCMC methods are based on an iterative updating scheme that is repeated until the sequence of parameter vectors converges. We first estimate the BBC model parameters by performing Gibbs Sampling using the WinBUGS statistical application Version 1.4.1 (MRC Biostatistics Unit 2004). Documentation for the WinBUGS application is available at www.mrc-bsu.cam.ac.uk. Using the same model structure and inputs, an alternative Bayesian method was used to verify the BBC model results obtained using WinBUGS. In contrast to the iterative Gibbs sampling method, Sampling-Importance-Resampling (SIR) is a noniterative Bayesian method. See the Prevalence document (Attachment 1) for details of the Bayesian Birth Cohort model, including the WinBUGS code and a description the SIR algorithm used to implement it.

III.A.3. Summary of assumptions and methods used in the Canadian calculations

Detailed explanation of the following assumptions and analytic methodology is included in Attachment 1.

1. As is true for many countries, precise data for age structure of the Canadian population is not known. However, the population structure was estimated based on data from Statistics Canada (http://www.StatCan.ca) and further verified by comparing the results with the age distribution predicted by the Harvard risk assessment for the U.S. population (Cohen et al. 2001; 2003). This distribution was then used for the "idealized" age distribution section of the BSurvE model.
2. BSurvE requires that the test data be stratified by age. However, prior to recent revisions to the OIE code (OIE 2006a), age stratification data were not an essential component of BSE surveillance, and thus were not routinely captured. In Canada, age associated data are available, however, for approximately 50 percent of the BSE tests undertaken within CFIA's TSE network laboratories in 2004 and 2005. This subset represents over 20,000 animals. Considering the large number of animals with age data and that there appeared to be no significant differences in age related trends between these years, age stratification estimates for each surveillance stream was determined by pooling the two years of data.

[12] Under OIE Terrestrial Animal Health Code 2006 Appendix 3.8.4, BSE surveillance points remain valid for 7 years (OIE 2006c).

These estimates were then used to stratify the surveillance results of animals for which age data were not available.

3. The December 2003 case discovered in the United States was included in the prevalence calculation as a Canadian case, however, no other surveillance data for Canadian cattle in the United States were included. Thus, the positive data point was included but none of the corresponding negative results were considered in this analysis. The inclusion of positive but not negative data from the United States acts to over-estimate the prevalence estimate for Canadian cattle.
4. BSE tests that were done as part of the epidemiologic investigations of BSE cases in Canada did not meet Canada's BSE surveillance criteria for the targeted sample population and were therefore excluded from the input data used to estimate the Canadian prevalence. Thus, only those samples that were collected for the purpose of Canada's BSE surveillance were included in the national prevalence estimate. Although the negative samples from healthy animals tested in the follow-up investigations were not used for estimating the prevalence of BSE in Canada, they do increase confidence that no unidentified cases are present in local association with the positive animals.
5. Under BSurvE, the exit constants are specified by cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) and BSE status of the animal. Until clinical signs develop, the age-dependent exit probability for infected animals is the same as for non-infected animals. For our estimates, these constants were set at the default of the BSurvE model which reflects the United Kingdom and European experience. They are primarily influenced by disease dynamics (BSurvE.com 2005) and are assumed to have minimal influence on North American assessments based on current knowledge of BSE.
6. Clinical suspects were identified from the Canadian surveillance database based on the clinical signs and history recorded by field veterinarians in the submission record. They were not defined by "submission reason" because this category could allow samples to be designated as clinical suspect without supporting information from the veterinarian. Sample submission data that reported clinical signs listed on the CFIA Web site as compatible with the clinical suspect definition were electronically selected from the CFIA database. The selected records were further reviewed by BSE epidemiologists from CFIA and USDA to remove animals with acute neurological conditions or other diseases that explained alternate diagnoses for the neurological signs reported. The final set of samples were those that met criteria described in the OIE code for classification as clinical suspect animals.
7. The initial UK ruminant feed ban substantially decreased the number of new cases in subsequent birth cohorts. Similar to the approach taken in estimating BSE prevalence in the United States (APHIS CEAH 2006), we assume that the Canadian feed ban during its first five years would reduce Canadian prevalence proportionately to the observed reduction in UK prevalence during the first five years of the UK ban: 1989 to 1994, during which the UK feed ban was most similar to the current Canada feed ban. We therefore incorporate evidence from

the UK reflecting the drop in prevalence following their feed ban into an estimate of Canadian BSE prevalence. We further note that as our knowledge of Canada's prevalence improves through continued surveillance efforts, the statistical contribution of the additional UK evidence diminishes.

8. Analysis of the Canadian BSE surveillance data provides no statistical basis for distinguishing BSE prevalence among birth year cohorts (Attachment 1). Therefore we calculated a single prevalence estimate for the entire population.

III.A.4. Results of prevalence estimation

The table below presents the expected prevalence estimates in the standing adult cattle population of Canada in 2006, as well as their respective 95th percent confidence levels[13]. The BSurvE "Prevalence B" estimate is presented for comparison because it is calculated without incorporating evidence about the effect of the feed ban beyond that reflected in the surveillance data. See Attachment 1 for details of the BSurvE model and inputs.

Table 3. Results of prevalence calculation.

Prevalence in adult population	Bayesian birth cohort method (BBC) with UK feed ban data	BSurvE Prevalence B estimate without including feed ban data
Expected value (mean)	$0.68*10^{-6}$	$3.9*10^{-6}$
95th percent confidence level	$1.1*10^{-6}$	$6.8*10^{-6}$

III.A.4.a. *Application of prevalence estimates to the Exposure Assessment*

It is important to note that the estimated prevalence distribution presented here represents parameter uncertainty. For a fixed prevalence value, the number of infected cattle in the population would still vary randomly over time. Assuming a constant probability of infection, the random variability in the number of BSE infected animals in the adult cattle population would follow a binomial distribution. For a large sample size and low prevalence values, the Poisson approximates the binomial variability distribution and is incorporated in the model supporting the exposure assessment for live bovines (Section IV.A. and Attachment 2) to represent variability around the prevalence estimates generated here.

Moreover, it is important to recognize that our models provide a robust estimate of the prevalence in Canada at this point in time. They do not project changes in prevalence expected in the future. Empirical evidence from the UK has demonstrated and simulation studies have reinforced that implementation of a ruminant to ruminant feed ban leads to continued decrease in prevalence over time (Cohen, et al. 2001; 2003; DEFRA 2006, EC 2003; 2005), yet the methods we use to estimate the prevalence of BSE in Canada cannot

[13] As used here, the term "confidence level" refers to the percentile of the uncertainty distribution (i.e., the 95 percent confidence level is the 95th percentile of the uncertainty distribution).

predict such future changes in prevalence. We can, however, use these August 15, 2006, prevalence estimates in two different ways. First, we can use them to provide a current estimate of possible release via live animal imports in the first year of our analysis, and we can qualitatively consider subsequent years of decreasing prevalence in our exposure assessment. Second, as we allow for less likely outcomes over the 20-year period of the analysis, we can also use these prevalence estimates as numeric surrogates for the release input parameter of the exposure model (Attachment 2), which we use to inform our exposure assessment (Section IV.A.).

Like the effects in the UK described in the Hazard Identification (Section II), similar effects of a feed ban have been seen in the EU. The apparent number of cases of BSE identified in the EU-15 Member States has decreased every year since 2001. Feed ban legislation was initially adopted within the EU in August 1994, and was gradually strengthened over the intervening years until the current requirements took effect in 2001. While the legislation took effect upon publication in 1994, it is recognized that initial implementation was inconsistent and some efforts were not immediately effective. In fact, this initial inconsistency, especially regarding cross-contamination, led to increasingly stringent feed ban requirements (EC 2003; 2005). Nevertheless, the implementation of active surveillance efforts within the EU in 2001 documents the effects of the initial feed ban. Allowing approximately 5-6 years before being able to observe the effects of the feed ban on diagnosed cases, the decreasing number of bovine cases reflects the impact of the initial feed ban. An alternative way to evaluate the effects of the feed ban is to observe the number of cases by year of birth. In the EU, the peak number of cases was born in 1995 followed by a significant drop, reflecting the effect of the feed ban (EC 2005a).

Given this demonstrated experience regarding the effects of a feed ban, it is extremely likely that the prevalence of BSE in Canada will continuously decrease over the next several years. The Canadian government has reached the same conclusion in their analysis and further predicts the ultimate eradication of the disease (CFIA 2004; 2006).

III.B. *BSE reduction factors for the various commodities proposed for importation from Minimal Risk Regions*

III.B.1. BSE reduction factors for live bovines

The OIE establishes standards for the international trade in animals and animal products. The OIE *Terrestrial Animal Health Code* (Chapter 2.3.13) allows trade in live cattle from regions that have reported BSE and have an effective feed ban in place, provided that the cattle were born after the date when the feed ban was effectively enforced.

As described in the Hazard Identification section of this document, BSE is spread under field conditions when cattle consume feed contaminated with the BSE agent. Transmission can be prevented by excluding potentially infected materials from ruminant feed. Therefore, bovines born after the date when a ruminant-to-ruminant feed ban was effectively enforced are unlikely to have been exposed to the BSE agent.

Although the amended rule addresses the importation of live bovines, we acknowledge that a very small proportion (roughly 2500 of 1.3 million, or 0.2 percent in the original risk assessment, and 12,000 of the roughly 1.3 million, or 0.9 percent, per the revisions of projections for the final rule), of these animals will be bison. Therefore, we focus this discussion on the impact of the "date of the effectively enforced feed ban" mitigation on cattle, rather than on bovines in general. We have no reason to believe that these conclusions do not also apply to bison, however.

In the sections that follow, we discuss the feed ban and related activities in Canada that mitigate the risk that cattle exported from Canada to the United States would be exposed to the BSE agent. Then, in order to increase the certainty that animals eligible for import to the United States have been subject to the fully implemented Canadian feed ban, and to be consistent with the OIE standard described above, we apply the gathered evidence to determine the date when we are confident that an effectively enforced ban was achieved.

As part of previous rulemaking, an evaluation was done that concluded that the feed ban was effectively enforced (APHIS 2004). This conclusion was based on consideration of the regulations in place based on statutory authority, adequate infrastructure to implement the regulations, and evidence of implementation and monitoring (i.e., compliance inspections, training and records).

After this determination was made, then consideration was given to the date when full implementation was achieved. Full implementation and effective enforcement is considered to be achieved after completion of the initial (or practical) implementation period and sufficient time has elapsed to allow most feed products to cycle through the system. The practical implementation period, which begins when the regulations are initially put in place, can be determined by evaluating implementation guidance and policies, such as allowing grace periods for certain aspects of the industry. In addition, the time necessary for initial education of industry and training of inspectors must be considered. After the practical implementation period was defined, then we considered a sufficient time period subsequent to this to allow most feed products to cycle through the system, given the management practices in the country.

In the following sections, we provide a detailed explanation for our choice of March 1, 1999, as the date the feed ban was effectively enforced. This date allows time for adequate implementation of the feed ban and for previously produced prohibited, potentially contaminated feed to be exhausted. Based on this evaluation, APHIS concludes that there is an extremely low likelihood that cattle born in Canada on or after March 1, 1999, will have been exposed to BSE.

III.B.1.a. *Feed ban in Canada*

As part of its analysis (APHIS 2004) for its 2005 rulemaking on BSE Minimal Risk Regions, USDA evaluated a series of measures introduced in Canada to prevent the feeding of ruminant proteins to ruminant animals. USDA considered the compliance activities reported by the CFIA as well as epidemiological information as evidence of the

effectiveness of the feed ban. The risk analysis concluded that compliance with the feed ban was good, and that the feed ban was effectively enforced.

In response to the detection of two additional BSE cases in Canada, in January 2005, USDA reassessed the oversight of Canada's feed ban. Based on review of inspection records and on-site observations, USDA confirmed that Canada has a robust inspection program, that overall compliance with the feed ban is good, and that the feed ban is reducing the risk of transmission of BSE in the Canadian cattle population (USDA 2005).

In addition to the USDA audit of the Canadian feed ban, CFIA conducted its own review in 2005, and concluded that the ban is providing an effective barrier that is contributing to reducing the BSE risk in the country to an extremely low level (CFIA 2005).

Canada's feed ban was also a central issue in an investigation conducted by the USDA in 2005 of the epidemiology of BSE in North America (USDA 2005a). In 2006, Canada released the assessment of the North American cases of BSE diagnosed from 2003 to 2005 (CFIA 2006). This report describes the epidemiological investigation of cases as well as their association with potential sources of infectivity. Information from the epidemiological investigations to date and the 2005 feed ban reports are incorporated into the elements of our discussion below regarding the efficacy of Canada's feed ban.

In June 2006, CFIA finalized regulatory amendments to enhance their feed ban. These require, among other things, the removal of specified risk materials from all animal feeds, pet food, and fertilizer. These regulations will not be effective until July 12, 2007, and therefore they are not considered in the following discussions.

III.B.1.a.1. *Implementation of the Feed Ban*

On August 4, 1997, Canada issued regulations prohibiting the use of mammalian protein in ruminant feeds as follows: "Any feed that is, or that contains any prohibited material originating from a mammal (with exceptions) shall not be fed to a ruminant" (CFIA 2002; Health of Animals Regulations, Part XIV, Sections 162-171). The ban provided exceptions for milk, blood, gelatin, and protein derived solely from porcine or equine sources. Canadian feed regulations also prohibit the use of plate waste[14] and poultry litter in ruminant feed. Canada's feed ban prohibits feeding of most mammalian proteins to ruminant animals, such as cattle, sheep and goats.

Elements of the feed ban include requirements for labeling and record-keeping. Feeds for equines, porcines, chickens, turkeys, ducks, geese, ratites or game birds, containing prohibited materials, must be clearly labeled with the following cautionary statement, "Do not feed to cattle, sheep, deer or other ruminants." Labels for bulk feed are stapled to the invoice and shipping documents. Ruminants may be fed pure porcine meal, equine meat meal and nonmammalian protein meal (fish, avian), as well as milk, blood, gelatin, rendered animal fat and any products produced from these materials from all species.

[14] Plate waste means any edible material originating from kitchens, restaurants, catering facilities or the household of the farmer or person tending the animals.

Feed manufacturers, renderers, retailers, and livestock producers must document their production procedures and feeding practices to verify their compliance with the feed ban. Feed manufacturers must keep records regarding the composition, identity, and distribution of all feeds for the species named in the regulations. Renderers, feed manufacturers and farmers must take steps to prevent the incorporation or cross-contamination with material prohibited under the feed ban into ruminant feed. To prevent the misfeeding of prohibited material to ruminants, users of livestock feed must keep labels or invoices from all purchased feeds containing prohibited material; these records must be kept for two years. Prohibited material may be fed to non-ruminant animals such as poultry and swine. CFIA expected that these practices and requirements would become more efficient and familiar over time as evidenced by the phase-in periods described below.

Beginning as early as 1996, as the ban was being formulated, government officials in Canada met extensively with feed mills and the rendering and livestock industries to educate and inform all sectors about the upcoming regulatory requirements (CFIA 2005). As noted above, Canada published its regulations banning prohibited material in ruminant feed on August 4, 1997.

Although the regulations came into force the same day, full implementation was a gradual process. From the outset, CFIA recognized that a phase-in period would be required before prohibited materials that were already in feed channels would be exhausted, and labeling and record keeping requirements would be met. It was estimated that it would take approximately 30 days for feed mills and retailers to use up and distribute existing supplies of "old" product (i.e., unlabeled feed intended for ruminants and produced using ruminant MBM); 60 days to add the caution statement to labels, invoices, and production records; and 60 days for farms to use up their stores of "old" product (USDA 2005a). All retailers were given until September 3, 1997, to use or distribute feed already produced. Feed manufactures received a grace period until October 3, 1997, to comply with labeling requirements. Livestock producers were given a grace period until October 3, 1997, to use the feed manufactured and purchased prior to the feed ban. However, feed tracing associated with the epidemiological investigations of one of the Canadian BSE cases suggested that feed produced prior to implementation of the feed ban may have been available at feed stores and/or on-farm several months longer than anticipated. Therefore, CFIA considered that the "practical implementation period" may have been up to 6 months after the date of the ban (USDA 2005a).

Implementation of the feed ban required addressing the four major components of the feed chain involving the use of ruminant derived proteins in animal feeds, and preventing cross contamination of cattle feed with prohibited material or misfeeding of prohibited material to cattle. Briefly, these components are the collection of inedible products from slaughter and/or dead stock and transport of these materials to the rendering plant; processing by the rendering plant of inedible material into products (primarily MBM) and transport to feed mills; mixing by the feed mill of the rendered products with grains and other ingredients into feeds for a variety of animals (the highest volume being used in

feed for poultry); and distribution to farms where these feeds may be used with or without further mixing. Specific control measures appropriate to each of these components had to be developed and incorporated into the feed ban requirements.

III.B.1.a.2. *Rendering industry*

The rendering industry is crucial in reducing the risk of transmitting BSE infectivity, not only because of its role in inactivation of the BSE agent, but also because it serves as a critical control point for the redirection of ruminant protein away from cattle feeds. Since 1998, all Canadian rendering facilities have been subject to annual inspections and permitting (USDA 2005). Three types of permits are issued, allowing companies to produce only non-prohibited material, only prohibited material, or both non-prohibited and prohibited material (USDA 2005). Permitting requires implementation of manufacturing controls (such as Good Manufacturing Practices and risk-based HACCP[15]), record-keeping (for both production and distribution) and labeling requirements ("Do not feed to cattle, sheep, deer or other ruminants" on labels and invoices for all prohibited material) directed at preventing cross-contamination or misfeeding.

III.B.1.a.3. *Addressing cross-contamination*

As mentioned earlier, renderers, feed manufacturers and farmers must take steps to prevent cross-contamination of ruminant feed with material prohibited under the feed ban. Such contamination can be prevented by having dedicated processing lines or facilities which use only prohibited or non-prohibited material. If a facility handles both prohibited and non-prohibited material, procedures must be established and maintained to conduct flushing and/or clean-out between batches of product to prevent cross-contamination.

Investigation of the BSE cases born in 2000 and 2002 suggest that these animals were most likely exposed during their first year of life to feed contaminated during processing (CFIA 2006b). In particular, the reports of the investigations identified incidents of concern in which ruminant feed was processed or transported immediately following the processing of non-ruminant feed containing prohibited material. Such incidents were in contravention of Canadian regulations, which require flushing and/or clean-out between batches if ruminant feed is processed on the same lines as feed containing prohibited material.

The detection of BSE in an animal born after the date the feed ban was implemented does not indicate an overall failure of the measures in place to reduce and eventually eradicate the disease from a country. In most other countries that have experienced cases of BSE, similar events have occurred. Nevertheless, despite such occurrences, a feed ban will be effective in decreasing the transmission of disease (Heim and Kihm 2003).

[15] HACCP is the frequently used acronym for Hazard Analysis and Critical Control Point, an approach to controlling hazards, such as food contaminants, in the manufacturing process.

The feed industry has taken a number of aggressive steps to comply with measures in the feed ban designed to reduce the risk of cross-contamination of feed for cattle with prohibited material. Recently, both the United States and Canada reviewed the changes made to industry procedures and government inspectional oversight to meet the feed ban requirements at feed mills and rendering facilities (USDA 2005; CFIA 2005). These reviews demonstrated, for example, that the rendering industry has moved toward establishment of dedicated facilities or dedicated processing lines within rendering facilities (USDA 2005; CFIA 2005). Of the 29 rendering facilities in Canada, six handle both prohibited and non-prohibited material. Of those six, four use dedicated processing lines (CFIA 2005). According to CFIA's reports, the feed manufacturing industry has also moved toward dedicated feed manufacturing facilities. Per the most recent review, 94 (17 percent) of the 550 commercial feed mills that handle prohibited material also manufacture feeds for ruminants (CFIA 2005). These actions, in addition to the labeling and record keeping requirements for all products containing prohibited material, decrease the likelihood of contamination of ruminant feeds with prohibited material. HACCP programs, certified through the Animal Nutrition Association of Canada, have been developed and implemented at commercial feed mills producing over 60 percent of total commercial feed production (McGrath 2004). Under these programs, feed mills have incorporated elements of the feed ban into their manufacturing process that are supported by additional training of employees, developing standard operating procedures, and maintaining appropriate records.

III.B.1.a.4. *Education and industry awareness*

The Canadian federal government, through the CFIA, is responsible for regulating and overseeing inspection of the animal feed industry. CFIA developed education and training initiatives shortly after the feed ban was first proposed in 1996 and began educating their own inspection force, as well as the feed industry, livestock producers, and veterinarians about the impending regulations and the steps necessary to implement them. The Feed Program Inspection Manual, the main training tool for CFIA inspectors, was supplemented with newly developed guidelines, standards and procedures to facilitate uniform implementation of the new feed ban inspection tasks. Inspections were increased. Workshops were held in all regions to cover the controls and processes required to comply with the feed ban's requirements (CFIA 2005).

Once the feed ban regulations were in place, CFIA continued to interact with and educate feed manufacturers, renderers, feed retailers, and producers to support implementation of the new regulations. These efforts included workshops; posting the new regulations on the CFIA Web site; and preparing and disseminating bulletins and press releases to all affected parties. Broad educational outreach by CFIA about BSE was made to government and private veterinarians, provincial, federal and university diagnosticians, producers, and workers involved in all aspects of the livestock industry (CFIA 2005). The cumulative effect of these educational efforts has been to support and enhance the effectiveness of the feed ban by ensuring that each sector of the impacted industry has taken the steps necessary to implement and sustain an effective feed ban, understand the

impact of BSE on Canadian agriculture, and eliminate exposure of the Canadian cattle population to BSE infectivity. It is likely that the high level of awareness fostered by CFIA at various levels facilitated the effective implementation of the feed ban.

III.B.1.a.5. *Inspections and compliance*

Once the new feed regulations had been introduced, communications with the affected industries broadened and CFIA implemented an inspection program. This program was introduced in phases. From 1997-2000, inspection activities focused on integrating the feed ban's requirements into standard industry practices. For example, since 1998, rendering facilities were required to pass an annual inspection in order to renew their permits to operate. In 2000 and 2001, CFIA modified its compliance programs by increasing the frequency of inspections of commercial feed mills from once every three years to every year and by continuing the annual inspection and permitting of all rendering facilities. Since 2002, CFIA has been conducting annual inspections of all rendering and commercial feed mill facilities and some ruminant feeders and retail feed distributors. There are approximately 20 feed mills per renderer and 400 livestock producers per feed mill. Because of the impact of each renderer or feed mill on so many producers, measures implemented by CFIA to prevent commingling or cross contamination of ruminant feed with prohibited materials directed at the rendering and feed manufacturing industries were essential for implementation of an effective feed ban. USDA has concluded that, in combination with labeling and record keeping requirements, these measures have continued to serve to prevent feeding of prohibited protein to cattle (USDA 2005).

III.B.1.a.6. *On-farm feeding practices contributing to feed ban efficacy*

To evaluate the implementation and effectiveness of the feed ban at the farm level, it is important to consider on-farm feeding practices. Most Canadian cattle are raised on either dairy farms or beef cattle operations. The nutritional requirements of dairy and beef cattle differ, and the nutritional needs of each vary by age and stage of production. Animal source proteins may be useful in the rations of dairy cattle to balance specific nutrients (lysine and other amino acids, calcium, and phosphorus) and supplement protein intake. However, a variety of plant proteins and animal protein alternatives from non-prohibited sources are available to Canadian producers including fish meal, porcine blood meal, feather meal, and processed soy products. Most cattle producers do not hold extensive long term inventories of purchased feeds on their farms due to limited storage space and expense. These practices make it unlikely that feeds containing prohibited material were available for more than a few months after the original implementation of the feed ban. The possible exception is mineral mixes produced before the feed ban that may have contained ruminant meat and bone meal. Mineral mixes are typically fed daily but in very small quantities (grams rather than pounds per day) (NRC 2001; NRC 1996) and may be stored on the farms for longer periods of time. We believe, however, that they are not likely to have been purchased for use for periods longer than a year.

Both beef and dairy cattle production can be considered to have an annual or 12-month cycle, in that a cow on a beef or dairy farm will generally give birth once a year. Calving occurs year-round on Canada's dairy farms to ensure a constant supply of fluid milk and the farms typically raise their own replacement heifers. Most dairy farms produce their own forage and grains (CFIA 2002). Forages produced seasonally are stored on the farm to provide the basis for the diet fed to dairy cattle of all ages and production stages. Protein supplements and specialty feeds, such as mixed calf feeds, are typically purchased commercially in quantities to be fed out over a few months because these supplemental feeds are expensive to purchase, costly to store, and may deteriorate with time. Typically, purchased feeds are available throughout the year with only moderate price variations, so there is little incentive for producers to maintain large on-farm inventories (Leger 2005 personal communication). The Canadian beef production cycle is very seasonal in that cows are bred so that calving occurs at the same time of year, general in the spring (CFIA 2002). Producers are not likely to carry extensive feed inventories from season to season (Gow 2005 personal communication). Therefore, in both dairy and beef production, a 12-month period would generally be sufficient to allow purchased feed products that may contain MBM to be completely used.

III.B.1.b. *Conclusions: BSE reduction factors for live bovines*

In its previous risk analysis (APHIS 2004), APHIS concluded that, at the time the analysis was conducted, Canada had an effective feed ban in place. However, that analysis did not attempt to establish a specific date on which the ban became effective. The feed ban comprises a number of interrelated measures that have a cumulative effect, and compliance with these measures continues to increase as the program evolves. In addition, since the implementation of the feed ban on August 4, 1997, CFIA has continued to revise and strengthen its processes and procedures to further enhance the effectiveness of the feed ban. APHIS concludes that all of these factors have resulted in an incremental reduction in the risk that Canadian cattle will be exposed to the BSE agent.

As discussed above, a "practical implementation period" of six months has been estimated for the feed ban to be fully implemented, making February 1998 a more realistic date on which the ban can be considered to have gone into effect. The likelihood that cattle born after that date would be exposed to the BSE agent decreases even further over time. APHIS considers that a period of one year following the full implementation of the feed ban allows sufficient time for the measures taken by Canada to have their desired effect. Therefore, APHIS concludes that there is an extremely low likelihood that cattle born in Canada on or after March 1, 1999, will have been exposed to the BSE agent via feed. Therefore, these animals have an extremely low likelihood of being infected, and thus can be imported into the United States for any purpose.

III.B.2. <u>BSE reduction factors for blood and blood products.</u>

APHIS proposes that blood and blood products from Canadian bovines be allowed to enter the United States under certain conditions. This section evaluates the factors that

reduce the likelihood of entry of BSE into the United States via these commodities, including the implementation of several required mitigations listed here. The blood and blood products must be from a clinically normal animal and, if harvested at the time of slaughter, the animal was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or to a pithing process. For fetal bovine serum (FBS), the mitigations are that the dam must pass ante-mortem inspection, the uterus must be removed from the dam's abdominal cavity intact and taken to an area separate from the kill floor for collection. All blood must be collected in a closed system.

Following the risk assessment format described in the Introduction, in this section we analyze the various nodes in the potential risk pathway for imported blood and blood products from Canada. We first provide justification for focusing our discussion on those products used in the production of veterinary vaccines and drugs. In keeping with the scope of this risk assessment, we are addressing only those pathways that may influence animal health[16]. The impact of BSE prevalence in Canada on the overall likelihood of release of infectivity into the United States will be integrated with the findings of this section in the release summary described in Section III.D.2.

III.B.2.a. *Scope of the analysis: relevant products*

Blood and blood products can be divided into two main groups: whole blood and cellular derivatives such as red cell concentrate, platelets, and other cellular elements; and plasma-derived products including serum (including FBS), clotting factors, immunoglobulins and albumin (Farshid, et al. 2005). Plasma is the cell-free portion of the blood. Serum is plasma with fibrinogen and clotting factors removed.

Because blood and blood products (or products manufactured with them) are typically delivered by injection, they present different risks than most other bovine products considered for import. Injection presents a different risk pathway than does oral consumption of BSE-contaminated bovine materials. The latter pathway is commonly evaluated in the cattle BSE literature. The route of exposure can affect the risk of disease transmission. The relative efficiencies of transmission have been reported to be, in decreasing order, intracerebral (IC), intravenous (IV), intraperitoneal (IP), subcutaneous/intramuscular (SC/IM), and oral/intragastric. In mouse scrapie models, it is estimated that the subcutaneous/intramuscular route requires 10,000 times the intracerebral dose required to produce infection (Prince, et al. 2003). The equivalent of 100,000 IC doses is thought to be necessary for infection by the oral/intragastric route (Prince, et al. 2003). We extrapolate from these data that mice exposed to scrapie via the IM or SC routes are 10 times more likely to become infected than those exposed orally. Therefore, we limit this assessment to the pathways in which these products can be used in animal vaccines and injectable drugs.

Of the various products listed above, only plasma-derived fetal bovine serum (FBS), also called fetal calf serum (FCS), and bovine serum albumin (BSA) derived from adult and

[16] The accompanying environmental assessment (APHIS 2006) must consider potential impacts of a proposed action on the human environment, including public health.

calf serum are used in significant amounts for the preparation of animal vaccines and drugs. Other products that could theoretically be used in the manufacture of animal drugs include cell-derived components such as hemin, hemoglobin, lymphocytes and platelets; and plasma-derived products, such as blood lipids, bovine immunoglobulins, clotting factors, cytokines, fibronectin, Fractions I-V (various proteins separated from plasma), hormones (e.g. serum gonadotropin), iron, and plasma protein (Popek 2005 personal communication). In practice, however, these items are not used in the manufacture of animal vaccines and drugs, limiting their role in the potential BSE risk pathway for animal exposure.

III.B.2.b. *Infectivity of blood and relevant blood products*

Experiments based on primary infection by the oral route have examined tissues from BSE-infected cattle. Although infectivity was identified in various tissues, primarily in the central nervous system, it was not demonstrated in a wide variety of other tissues. Specifically relevant for this discussion is the fact that no BSE infectivity was demonstrated in cattle blood or any tested derivatives (EC SSC 2002, Espinosa, et al. 2007). This conclusion derives from studies in which tissues from infected cattle were injected intracerebrally (IC) and intraperitoneally (IP) into mice (the "mouse bioassay"), or IC into cattle (the "cattle bioassay"). Mouse bioassays were performed using buffy coat (the white cell fraction of centrifuged whole blood), clotted blood, fetal calf blood and serum from confirmed clinical cases (Kimberlin 1996 cited in EC SSC 2002). Mouse and cattle bioassays were performed on buffy coat from cattle experimentally exposed orally to the BSE agent. In all cases, no evidence of infectivity was detected.

Because no evidence of infectivity has been found in cattle blood or the components listed here, we could end this portion of the release assessment at this point. However, we acknowledge that the route of exposure – injection vs. oral consumption – warrants further consideration. We also recognize that additional processing steps may have further mitigative effects, and therefore, should be presented. However, presenting direct evidence for the effects of processing of bovine blood on the persistence of BSE infectivity is not possible because infectivity is not detectable even in unprocessed bovine blood. Thus, although APHIS generally avoids extrapolating from studies of TSEs in other species, in order to utilize the only available evidence, we have elected to incorporate such information here. Thus, we cautiously use studies on TSEs in other species as potential indicators of the behavior of BSE in cattle blood if it were to be present in previously undetectable levels.

Investigators have demonstrated that BSE can be transmitted to sheep by transfusion of whole blood from sheep experimentally infected with BSE (Houston, et al. 2000; Hunter, et al. 2002). In these studies, a transfusion of 400 ml of whole blood, taken from clinically normal infected sheep, caused disease in 2 of 24 recipients. Blood or buffy coat taken from clinically ill animals, however, did not cause disease in the 4 recipients. These same investigators also examined scrapie in sheep. A total of 4 sheep out of 21 transfused with blood from sheep naturally infected with scrapie developed disease. The transfusion of buffy coat derived from a clinically ill animal caused disease in the

recipient. The Scientific Steering Committee of the European Commission examined these studies and their implications. They concluded that the finding of infectivity in the blood of sheep could not be extrapolated to BSE in cattle (EC SSC 2002a).

Brown, et al. (1999) using a human strain of TSE (Gerstmann-Straussler-Scheinker, or GSS) in mice inoculated intracerebrally, concluded that infectivity was present in the buffy coat (platelets, white cells) during the preclinical phase of TSE, but absent or in only trace amounts in the plasma or plasma fractions. Following the onset of clinical signs, increased infectivity of both buffy coat and plasma was found, but still very low compared to levels in the central nervous system. As cited in a review of the relevant literature (Comer 2004, p. II.18), most studies using a rodent model and adapted strains of scrapie or CJD demonstrated that the fractions containing white blood cells have the highest levels of infectivity.

In contrast to investigations of the natural distribution of infectivity in rodent blood fractions, one "spiking" study added high levels of hamster-adapted scrapie infectivity from brain homogenate to normal human blood. Following fractionation by centrifugation into red cells, white cells/platelets, and plasma components, titrations indicated that the majority of infectivity was in the red cell component (Brown, et al. 1998). These results, although not as relevant to understanding the natural distribution of TSEs in blood, may potentially apply to the distribution following cross-contamination at blood collection. Therefore, if contrary to current research, or if the proposed mitigations are not properly implemented, any BSE infectivity is present in bovine blood, either naturally or via cross-contamination, it would likely be highest in the cellular components. These fractions, both red and white cells, are excluded when harvesting FBS and BSA used in the preparation of vaccines and drugs.

Further decrease in TSE infectivity occurs with fractionation of plasma proteins. Fractionation is the process whereby specific proteins, such as albumin, are separated out from other components of the plasma. Infectivity in various fractions has been examined. For example, using data from several cited studies Comer (2004) estimated that human albumin contains $3.1x10^{-5}$ vCJD ID_{50}/gram. Compared to Comer's estimates of infectivity in whole blood (2 iv vCJD ID_{50}/gram), this figure represents a dramatic decrease.

In conclusion, the available evidence indicates that TSEs in other species, when found in the blood, are localized primarily to the cellular fractions. Although BSE has never been detected in any bovine blood or blood product, we expect even further risk reduction after removal of cellular fractions in the preparation of the most commonly imported bovine blood commodities.

III.B.2.c. *Likelihood of maternal transmission of BSE*

As discussed in Section II.A. of the Hazard Identification portion of this document, the likelihood of maternal transmission is extremely low. Therefore, for FBS and other fetally-derived products, maternal transmission represents an additional risk-reduction

step. If, despite evidence to the contrary, maternal transmission of BSE were to occur, infectivity is unlikely to localize to the fetal blood, just as it is unlikely to localize to adult blood.

III.B.2.d. *Mitigations to prevent contamination at collection*

Although we have demonstrated that BSE infectivity is not likely to localize to the adult or fetal blood, we recognize the possibility of cross-contamination with infective tissues, or SRMs at the time of collection, particularly in a slaughter environment. Certain slaughterhouse stunning practices – specifically the use of devices that inject compressed air or gas into the cranial cavity or pithing processes - may introduce macro-emboli of CNS tissue into the circulatory system (Anil et al., 1999; Schmidt et al., 1999). In addition, collection of blood in an open manner may allow other tissues to contaminate the blood. For example, pieces of spinal cord or other risk tissues could fall into an open container, such as a bucket or tub, if collection and pooling of blood from several animals is done in a slaughterhouse environment.

In order to prevent contamination due to such potential sources of infectivity, APHIS proposes the following mitigations:

For all blood:

1. the blood is collected in a closed system.

For blood collected at slaughter, the slaughtered animal:

2. must pass ante-mortem inspection and
3. was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process

For fetal bovine serum:

4. the dam must pass ante-mortem inspection and is not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process
5. the uterus is removed from the dam's abdominal cavity intact and taken to an area separate from the kill floor

For blood collected from live donors:

6. the donor must be free of clinical signs of disease

III.B.2.e. *Conclusions: BSE reduction factors for bovine blood and blood products*

Based on the evidence presented above, we conclude that bovine blood is highly unlikely to contain BSE infectivity, the fractions that are likely to be commercially exported are highly unlikely to contain infectivity, and that USDA-specified mitigations will prevent cross-contamination.

III.B.3. BSE reduction factors for small intestine other than distal ileum.

In this section, we qualitatively assess the factors that reduce the likelihood of BSE infectivity being released into the United States via the importation from Canada of bovine small intestine other than the distal ileum. We examine the factors acting at the various steps, or nodes, in the risk pathway. These factors include the distribution of infectivity to the small intestines, and mitigations to ensure proper removal of the potentially infectious distal ileum.

III.B.3.a. *Infectivity of the small intestine*

The evidence presented below demonstrates that the only portion of the cattle intestine in which BSE infectivity has been found in any assay is the distal ileum. We describe the most relevant observations regarding the pathogenesis of BSE in the gastrointestinal system of cattle experimentally and naturally exposed to the BSE agent.

- Pivotal studies of the BSE agent include experimental investigations of the pathogenesis of BSE after oral exposure of cattle. The experimentally exposed animals received a dose of infectivity that was 10 to 100 times greater than most cattle that have been naturally exposed via contaminated feed. In these studies, investigators examined the distribution of the agent in the lymphoreticular system, the peripheral nervous system, the central nervous system, striated muscles, and major viscera at various times after exposure (Wells, et al. 1996). Infectivity in bovine tissues was first assayed in the mouse bioassay, a procedure in which the agent is injected intracerebrally and intraperitoneally into certain nontransgenic strains of mice (Wells, et al. 1996; 1998) which are then observed for development of clinical signs. Results from the mouse bioassay demonstrated infectivity in the distal ileum of cattle from 6 to 18 months and from 36 to 40 months after oral exposure. No infectivity was detected at any time in the esophagus, reticulum, rumen, abomasum, proximal small intestine, proximal colon, distal colon, and rectum (EC SSC 2002b). In later studies, the same tissues were assayed for infectivity by intracerebral inoculation of cattle, a more sensitivity assay method (EC SSC 2002b). The cattle bioassay confirmed that the agent could be recovered only from distal ileum at times previously reported in the mouse bioassay.

- Studies examining the distribution of PrP^{Sc} by immunohistochemistry[17] in the distal ileum of infected cattle confirmed that PrP^{Sc} accumulated in Peyer's patches of the distal ileum at 6, 10, 14, 18, 36, and 40 months after exposure (Terry, et al. 2003). These findings were consistent with results from the mouse bioassay.

- No PrP^{Sc} was detected by immunostaining in the duodenum, jejunum, cecum, colon, myenteric plexus, and submucosal plexus of calves orally exposed to large

[17] We note that detecting the presence of PrP^{Sc} is not the same as demonstrating infectivity. There are many variables that contribute to infectivity, and while detecting PrP^{Sc} may indicate that infectivity could be present, it does not, by itself, indicate that it is indeed present.

doses of the BSE agent and killed 6 months after exposure (Terry, et al. 2003). In contrast, immunostaining of follicles from Peyer's patches of the distal ileum did reveal the presence of PrP^{Sc} in these same calves.

- The distal ilea of 29 naturally occurring cases of BSE were examined for PrP by immunohistochemistry. Sparse PrP^{Sc}-specific immunostaining was observed in neurons of the myenteric plexus of the distal ileum of nine of the cattle. No immunostaining in the submucosal plexus of the distal ileum of any of the infected cattle was observed, suggesting a very low level of infectivity in the enteric nervous system in the clinical phase of BSE (Terry, et al. 2003).

In summary, BSE infectivity has been found in the distal ileum of experimentally exposed cattle and not in other sections of the intestine. In addition, in naturally occurring cases, sparse immunostaining has been observed in the myenteric plexus of the distal ileum. Since the myenteric plexus extends throughout the small intestine, we acknowledge the possibility that infectivity might exist in the myenteric plexus of the jejunum or the duodenum. However, if infectivity in intestinal tissues (other than distal ileum) exists, it is below the level of detection by both the mouse and cattle bioassay. Given the relative efficacies of these experimental modes of transmission compared to oral exposure at doses estimated to have occurred in the field, we conclude that intestine other than the distal ileum is highly unlikely to contain epidemiologically-significant levels of infectivity, if any infectivity is present at all.

III.B.3.b. *Likelihood of improper removal of the distal ileum*

As discussed above, the distal ileum is the only portion of the bovine intestine in which BSE infectivity has been found in experimentally and naturally infected cattle. Although infectivity has not been detected in the rest of the small intestine, the complete removal of the distal ileum is essential to ensure that imported bovine intestine does not include a potential source of BSE infectivity. In this section we describe the anatomic relationships between the relevant parts of the bovine intestine and the mitigations designed to prevent inadvertent contamination of otherwise BSE-free tissues.

III.B.3.b.1. *Relevant anatomy of bovine small intestine*

The small intestine of cattle attaches at its most proximal end (closest to the mouth) to the most distal (closest to the anus) chamber of the ruminant stomach. This most proximal segment of the small intestine is the duodenum. Distal to the duodenum is the very long jejunum. According to the North American Natural Casings Association, the duodenum and jejunum are used for natural beef casings (NANCA 2004). Distal to the jejunum is the ileum, which is estimated to be two to three feet long (NANCA 2004). The distal-most portion of the ileum, or "distal ileum," is estimated to be 12 to 18 inches long. It attaches to the most proximal portion of the large intestine, the cecum, at what is termed the "ileocecal junction" or "ileocecal orifice." Just distal to the ileocecal junction is the cecocolic junction.

III.B.3.b.2. *Mitigations to exclude distal ileum from imported small intestine*

Since the distal ileum is the only portion of the small intestine demonstrated to contain BSE infectivity, its exclusion would remove any associated infectivity from the rest of the small intestine. In this section, we discuss the mitigations required to adequately remove the distal ileum.

USDA Food Safety Inspection Service (FSIS) and HHS Food and Drug Administration (FDA) have determined that the distal ileum can be effectively removed from the rest of the small intestine. They have also determined that the remaining small intestine can be used as human food if the distal ileum is removed (FSIS 2005, FDA 2005). To ensure the complete removal of the distal ileum, both FSIS and FDA require the removal of at least 80 inches of the uncoiled and trimmed small intestine as measured from the cecocolic junction (FSIS 2005, FDA 2005). Their regulations also allow for the facility to submit an equivalent process to the respective agency for approval. Based on the description of bovine intestinal anatomy, above, we concur that removal of this tissue will exclude the distal ileum.

An authorized veterinary official of the Government of Canada will be required to certify that any product containing bovine small intestine does not include distal ileum as defined above. This certification will ensure that conditions in Canada meet the standards that USDA considers appropriate for safe trade in this commodity.

III.B.3.c. *Conclusions: BSE reduction factors for bovine intestines*

The studies described above provide evidence that the distal ileum, but not the remainder of the bovine intestine, is a potential source of BSE infectivity. The distal ileum is the only portion of the bovine intestine for which OIE recommends any trade restrictions because of BSE (OIE 2006a). Similarly, both the Food and Drug Administration (FDA 2005) and the FSIS (FSIS 2005) have concluded that if the distal ileum is removed from the small intestine of cattle, the remainder of the small intestine can be used for human food.

Because bovine intestinal tissue, excluding the distal ileum, has not been shown to contain infectious levels of the BSE agent, even if derived from infected cattle, and because the distal ileum can be removed at slaughter in a manner to avoid contamination, APHIS concludes that it is highly unlikely that any bovine intestines imported from Canada into the United States would contain BSE infectivity.

III.C. *Projections and composition of cattle imports from Canada under the proposed rule*

In section III.A., we present results of a modified, previously published model (BSurvE) that estimates the BSE prevalence in Canada's standing (August 2006) cattle population. Because we cannot predict the rate at which prevalence in Canada may drop following

the implementation of their feed ban, we make the risk-inflating assumption that prevalence remains constant over the 20-year time horizon of the analysis. We then combine these prevalence values with cattle import projections to provide inputs into the quantitative exposure model. Because the revised Harvard model used to inform the exposure assessment tracks BSE infectivity from the time an animal is slaughtered, it requires that the number of animals imported annually for each age and use type (e.g., dairy, beef breeding, slaughter, etc.) be included as model inputs. In this section, we explain how these projections were prepared by USDA's Economic Research Service (ERS). In Section III.D.1. (BSE release via import of live bovines), we combine these projections with the prevalence estimates to express the likelihood of release that may be expected under particular scenarios.

The following tables represent the projections prepared in 2006 for the original risk assessment (APHIS 2006a) published with the proposed rule and used to inform the exposure model (APHIS 2006c). Updated projections used in the Regulatory Impact Analysis for the final rule are presented in the Updates section on pages 13-16. In that section, we demonstrated that the updated import projections do not lead us to challenge our earlier release conclusions.

Source of cattle import projections

The projected imports by age and use class were prepared for APHIS by USDA ERS. These values are based on USDA Baseline projections, with specific factors considered based on the regulatory changes outlined in this rule.

The USDA Baseline provides 10-year projections for the agricultural trade sector. Projections cover agricultural commodities, agricultural trade, and aggregate indicators of the sector, such as farm income and food prices. These projections assume no shocks and are based on specific assumptions regarding the macro economy, agricultural and trade policies, the weather, and international developments. They assume normal weather, no outbreaks of plant or animal diseases, and include short-term projections from USDA's *World Agricultural Supply and Demand Estimates* reports.

Each year, USDA Baseline projections are updated between October and December, and reflect a composite of model and judgment-based analyses. Beginning in August, macroeconomic and policy assumptions are developed. These assumptions are input into a large country commodity trade model called the Country-Commodity Linked System. This model covers 44 commodities and 32 countries and regions. Workshops are held in September and October, and the model results are presented to USDA's World Agricultural Outlook Board committee members. Model inputs are adjusted to reflect comments from the committee members. The final set of model outputs are used in the budget development process.

The baseline projections include values for important variables for the Canadian cattle and beef sectors, including Canadian cattle inventory and cattle exports. These values were used as the starting point in developing the import projections, with changes built

around these based on the current regulatory changes and subsequent effects on cattle and beef markets.

Breeding cattle imports are expected to return to historic patterns with the current regulatory changes. Between 1990 and 2002, less than 5 percent of the cattle exported from Canada (less than 0.5 percent of the Canadian cattle inventory) were breeding cattle. Dairy cows and heifers traditionally represented the greatest majority – almost 90 percent – of cattle in this grouping.

Estimating the quantities of cull cattle (slaughter cows, bulls, and stags) that would be imported was complex due to the age restrictions imposed by the rule. A culling age distribution was developed to determine how the availability of cull animals might change. Statistics Canada reports total Canadian cattle inventories and the percentage of animals born prior to 1999. The culling age distribution was calibrated around these percentages, with culling rates declining for each successive year's breeding herd cohort (other than for a notable culling of heifers and one-time cows that fail to become pregnant). Most dairy cows are culled by the time they have completed their fourth lactation, as milk productivity declines with cow age.

Regulatory restrictions on the importation of Canadian beef derived from older slaughter animals were also considered in developing the import projections. U.S. import restrictions on beef and beef products from Canadian animals slaughtered at 30 months or older have limited the value of this product in Canada and hence the price Canadian packers pay for cull animals. Canadian cull cow slaughter has increased as a proportion of all slaughter in Canada since U.S. import restrictions were initially imposed in 2003. Canadian cow slaughter has been particularly high since July 2005, when U.S. import regulations were implemented that allowed feeder and slaughter animals less than 30 months of age. Canadian cow prices have increased since late 2003; however, the U.S.-Canadian price differential is still wider than what was seen prior to May 2003, and this affects the import projections at least in the short term. In summary, the cull cattle projections are a function of the size of the total Canadian herd, historic import rates, and cull cattle's share of total imports. These quantities are then adjusted to reflect the age restrictions and any changes to the restrictions on imported beef and beef products.

The cattle categories subdivided by purpose (immediate slaughter, feeding for slaughter, and breeding), age and gender, and their respective import percentages, shown in Table 4, are discussed here briefly.[18]

[18] Updated analysis for 2007 by ERS projects lower initial cattle imports and changes the average breakdown across classes (discussed in Updates section, pages 13-16).

Table 4. Projected percentages of cattle imports from Canada with the proposed rule‡		
	Percentages	
	Sub-group	Overall
Slaughter cattle		82
Steers/heifers*	53.2	
Cows	21.1	
Bulls and stags	3.9	
Calves*	3.7	
Stockers/feeders*		13.8
Breeding cattle		4.2
Dairy heifers/cows*	3.6	
Beef heifers/cows*	0.4	
Bulls*	0.2	
Total		100

‡Updated projections are presented in Table ii in the Updates section, page 14. Our original conclusions regarding the likelihood of release of BSE are not sensitive to these data updates.
*As described in the following paragraphs, most of the animals in these categories would be less than 2 years of age at the time of import.

III.C.1. Slaughter Cattle

In the quantitative and qualitative approaches to the exposure assessment, which were based on the 2006 import projections, we assumed the following: Slaughter cattle, which would comprise up to 82 percent of the cattle imported, are slaughtered almost immediately after crossing the border. They were expected to have a somewhat older age distribution for the first year that the rule would be in effect (we assumed for this analysis that this would occur in 2007), with most of the surplus inventory eliminated by year end.[19]

Slaughter cattle can be categorized into 1) steers[20] and heifers[21]; 2) cows, bulls and stags[22]; and 3) calves[23] (USDA ERS 2004; Purdue 2006). Based on the 2006 projections used in the model, steers and heifers are the largest category, and would comprise about 53 percent of imports. In both the United States and Canada, slaughter steers and heifers are generally on feed from 120 days to more than 200 days before slaughter. Most of them are between 16 and 24 months of age at slaughter, with some over 26 months.

[19] Based on ERS' revised 2007 projections, most of this surplus inventory would not enter the United States because of age verification requirements. These changes are described in the Updates section, pp. 13-16.
[20] Steers are bovine males castrated prior to sexual maturity.
[21] Heifers are bovine females that have not yet given birth.
[22] Stags are male bovines castrated at or near maturity.
[23] Calves are young male or female bovine animals under one year of age.

Because more females than males are kept in the population for breeding (Matthews and Short 2001), we expect approximately 60 percent of this sub-group of slaughter cattle to be steers and 40 percent to be heifers. Historically, the percentage of steers has ranged from 53 to 65 percent, depending on the level of heifer retention for the Canadian breeding herd.

Based on the 2006 projections, slaughter cows were assumed to comprise roughly 21 percent of imports. Approximately 60 percent of these would be dairy cows. Their median age would be approximately 3.8 years, with most between 3 and 6 years of age. Slaughter beef cows would average 6 years of age, with most between 5 and 7 years of age.

Slaughter bulls and stags were assumed to comprise less than 4 percent of imports. Most are 5 to 7 years of age, with a median age of approximately 5.5 years.

Vealers and light calves would also comprise less than 4 percent of imports. They include cattle from less than 1 month old up to 8 months, with most between 4 and 5 months of age.

III.C.2. Feeders/stockers

Based on the 2006 projections, weaned steers and heifers (about 9 months of age) and yearlings (mostly 12 to 15 months of age) imported for feeding constitute the second largest group after slaughter cattle, about 14 percent of the overall total. This category is also the most variable, having ranged from 3 percent to 46 percent of Canadian cattle imports. The wide range is due to varying weather/forage conditions, feed costs, and inventory changes reflecting the cattle cycle. These cattle are all destined for feedlot finishing and slaughter, but may be placed on pasture for several months of gain before feedlot placement. They are generally placed on feed for 120 to over 200 days before being slaughtered.

III.C.3. Breeding cattle

Breeding animals were assumed to comprise approximately 4 percent of imports. They are destined for dairy and beef breeding herds and would be eventually culled like their U.S. herd mates. Dairy heifers and cows constitute the largest share of breeding cattle. They are mostly bred (pregnant) heifers that are 15 to 19 months of age and due to calve. They enter the milking herd at about 24 to 26 months of age. Young, open (not pregnant) dairy heifers and a small number of cows that have calved complete this category.

Beef heifers and cows would comprise less than 1 percent of imports and, like the dairy breeding stock, would include open and bred heifers and cows.

Bulls for breeding would constitute a very small proportion of total imports. This category includes beef bulls 15 to 24 months of age, as well as a few dairy bulls.

ERS has estimated the total projected number of animals to be imported for 2007 (the year in which we anticipated implementing the rule) through 2026 to provide twenty years of input data to be incorporated into the exposure model informing the exposure assessment below. These total annual projections are broken out into the various use categories in Table 5 below.

Table 5. Projected imports of various cattle use types for years 2007 through 2026. ‡

CASE: shares based on sum of annual imports over 1992-2003															
				Projected cattle imports to US from Canada, by category -- 1,000 head											
	Canadian			U.S.	SLAUGHTER CATTLE					BREEDING CATTLE				Stocker/
	Inventory	Pct	Pct		Steers &	Cows	Bulls	Vealers /	Sub-	Dairy cows	Beef cows	Bulls	Sub-	feeders
YEAR	,000 hd.	change	exported	,000 hd.	heifers		& stags	Light calves	total	/ heifers	/ heifers		total	(male+fem)
2007	14,400	97.1	9.5	1,368	728	289	54	51	1,121	50	5	3	58	189
2008	14,050	97.6	9.0	1,265	673	267	50	47	1,036	46	5	3	53	175
2009	14,250	101.4	8.5	1,211	644	255	48	45	993	44	4	3	51	167
2010	14,300	100.4	9.0	1,287	685	271	50	48	1,055	47	5	3	54	178
2011	14,375	100.5	9.0	1,294	688	273	51	49	1,060	47	5	3	54	179
2012	14,450	100.5	9.0	1,301	692	274	51	49	1,066	47	5	3	55	180
2013	14,550	100.7	9.0	1,310	697	276	51	49	1,073	47	5	3	55	181
2014	14,650	100.7	9.0	1,319	701	278	52	49	1,081	48	5	3	55	182
2015	14,250	97.3	9.5	1,354	720	286	53	51	1,110	49	5	3	57	187
2016	14,100	98.9	9.5	1,340	713	283	53	50	1,098	49	5	3	56	185
2017	14,425	102.3	9.0	1,298	691	274	51	49	1,064	47	5	3	55	179
2018	14,500	100.5	9.0	1,305	694	275	51	49	1,070	47	5	3	55	180
2019	14,650	101.0	9.0	1,319	701	278	52	49	1,081	48	5	3	55	182
2020	14,875	101.5	9.0	1,339	712	282	53	50	1,097	49	5	3	56	185
2021	15,200	102.2	9.0	1,368	728	289	54	51	1,121	50	5	3	58	189
2022	15,350	101.0	8.5	1,305	694	275	51	49	1,069	47	5	3	55	180
2023	15,450	100.7	8.5	1,313	699	277	52	49	1,076	48	5	3	55	182
2024	15,650	101.3	8.0	1,252	666	264	49	47	1,026	45	4	3	53	173
2025	16,000	102.2	8.0	1,280	681	270	50	48	1,049	46	5	3	54	177
2026	16,000	100.0	8.5	1,360	724	287	53	51	1,115	49	5	3	57	188

‡ Updated projections are presented in Table iii in the Updates section, page 15. Our original conclusions regarding release of BSE are not sensitive to these data updates.

Source: Expert opinion, USDA Economic Research Service, Market and Trade Economics Division, Animal Products, Grains, and Oil Seeds Branch. Based on "USDA Agricultural Baseline Projections to 2015," United States Department of Agriculture, Interagency Agricultural Projections Committee, Baseline Report OCE-2006-1, February 2006, http://www.usda.gov/oce/commodity/ag_baseline.htm; and import data 1992-2003; and projected Canadian inventory.

III.C. 4. Projected bison imports

Table 6. Projected bison imports to United States from Canada by usage category‡

YEAR	Canadian Bison Exports to United States	Slaughter	Breeding	Stocker/Feeders
2007	4,000	2,500	250	1250
2008	3,150	2,400	250	500
2009-2026	2,500	2,000	250	250

‡ Updated projections are presented in Table iv in the Updates section, page 16. Our original conclusions regarding the likelihood of release of BSE are not sensitive to these data updates.
Source: ERS Market and Trade Economics Division, Animal Products Branch.

Based on Department of Commerce, Bureau of the Census import data from 1996-2002, the ERS Market and Trade Economics Division, Animal Products Branch estimated the composition of projected bison imports. Because of restrictions on the movement of bison from Canada into the United States, they anticipated a higher number of exports in 2007 and 2008 than for subsequent years. From 2009, approximately 2500 bison were projected to be imported per year, with the following breakdown across three usage types. The numbers per usage type per year are presented in Table 6 and the overall breakdowns are described below:

Slaughter Bison

The primary share of the imports, 80 percent, is likely to be for immediate slaughter. About 80 percent of these imports are male, 5 percent female and about 15 percent unknown.

Breeding Bison

Of the 2500 bison expected to be imported per year, approximately 10 percent are for breeding purposes. Roughly 70 percent of these animals are female and 30 percent male. These imports provide a source of genetic diversity to the U.S. bison herd.

Feeder Bison

Feeders comprise about 10 percent of imports, of which roughly 90 to 95 percent are male.

III.D. *Release conclusions*

In the preceding sections of the release assessment, we have presented several pieces of evidence that were considered in determining the likelihood of release. In the Updates section (pp. 11-18), we demonstrate that including more recent BSE surveillance data from Canada and revised import projections does not alter the release conclusions presented here.

III.D.1. BSE release via import of live bovines

In section III.A., we present results of a modified, previously published model (BSurvE) that estimates the BSE prevalence in Canada's standing (August 2006) cattle population. Because of uncertainty in various parameters and constraints of the model itself, it incorporates some important simplifying assumptions that likely overestimate the prevalence values. For example, the positive test result from the case of Canadian origin that was diagnosed in the United States was included among the positive surveillance results (numerator), whereas negative and clinically normal animals of Canadian origin exported to the United States were not included in the population total (denominator). This approach likely inflates the Canadian prevalence estimates.

We consider the potential release of BSE over an extended period of time, assuming that the regulation would apply into the foreseeable future. In order to allow sufficient time for several potential amplification cycles (roughly 5-7 years each), we have evaluated release over a 20-year period: 2007-2026. We considered different scenarios for release, providing both qualitative and quantitative inputs to inform the exposure assessment.

In section III.B.1, we discuss the proposed mitigation of limiting animals intended for import to those born after the date the feed ban was effectively enforced. The evidence presented about the feed ban and related activities in Canada support the conclusion that cattle born in Canada on or after March 1, 1999, will have an extremely low likelihood of being exposed to, and thus infected by, the BSE agent. This conclusion contributes to the qualitative inputs evaluated in the exposure assessment. As further described below, however, data limitations prevent quantitative consideration of this mitigation.

As noted previously, our prevalence estimates are for the standing cattle population in August 2006. As described in Section III.A., implementation of a ruminant feed ban results in decreasing BSE prevalence over time (DEFRA 2006, EC 2005a; Cohen, et al. 2001; 2003; Cohen and Gray 2005). The methods we use to estimate prevalence, however, cannot project the changes expected over the 20-year period of our analysis. Therefore, we infer that the BSE prevalence and subsequent release of infectivity from Canada for each of the 20 years after the anticipated implementation of the amended regulation (initially estimated as 2007) are less than expressed by our quantitative estimate. We use these prevalence estimates in the exposure assessment in two different ways. First, we use them to provide a current estimate of possible release via live animal imports in the first year of our analysis, and then we qualitatively consider the most likely scenario of decreasing prevalence over subsequent years. Second, as we allow for less likely outcomes, we use these prevalence estimates as risk-inflating numeric surrogates for the release input parameter of the exposure model (Attachment 2) used to inform our exposure assessment.

Using the methods described in Section III.A., we have two estimates of expected (mean) prevalence in the Canadian herd for August 2006. One estimate (BSurvE), based on the accumulated Canadian BSE surveillance data, expresses the expected prevalence as $3.9*10^{-6}$ infected cattle. When combined with import projections for 2007 from Table 5

in Section III.C., this estimate predicts that less than 6 of the over 1.3 million animals projected to be imported that year will be infected (Table 7). This value is higher than that for nearly all other years in the analysis because, as seen in Table 5, 2007 is a year in which a relatively large number of animals was projected to be imported. Therefore, the values for 2007 reflect the highest number of "expected" infected animals.

The other estimate (BBC) of the August 2006 BSE prevalence in Canada incorporates both prior surveillance data and evidence from the UK on the impact of a feed ban. Given that Canada has an effective feed ban, as described in Section III.B.1., this estimate is likely the more realistic over the 20-year time frame of the analysis. Moreover, since imported live bovines from Canada must be born after the date of effective implementation of the feed ban, this lower estimate (expected value=$6.8*10^{-7}$) is far more applicable to the amended regulation. Using this approach, as indicated in Table 7,[24] we "expected" roughly 0.94 infected animals in that year. Once again, this prediction is for 2007, a year in which our import projections predicted higher volumes, and therefore compared to the subsequent 19 years, represents the highest number for this prevalence estimate.

Furthermore, the two prevalence estimates are calculated for the total cattle population in Canada, including cattle born before the date which APHIS concludes that the feed ban was effectively enforced. Because of data limitations, we did not calculate the prevalence by birth cohorts. Epidemiological evidence in the UK suggests that cohorts born after effective implementation of the feed ban are much less likely to develop disease than cohorts born before the effective implementation of such a ban (DEFRA 2006). Therefore, Canadian cattle born after the date the feed ban was effectively enforced are much less likely to be exposed to infective material and become infected with BSE. This evidence is considered in the qualitative evaluation of the most likely scenario in which prevalence in Canada decreases over the next 20 years. However, this evidence is not considered in the less likely scenarios represented in the quantitative analysis. In those scenarios, we assume that all animals are equally likely to have been exposed to infective material and that the prevalence remains constant over the next 20 years.

As noted in the import projections, the majority of imports are expected to be less than two years of age at the time of import.[25] Therefore, in 2007, this large group of younger animals would be born many years after both the initial implementation of the feed ban, and the date at which we consider the ban to have been effectively enforced. In subsequent years, these animals would be born an increasingly longer time after those dates. Therefore, they would be even less likely to have been exposed to infected feed.

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[24] See the updated Table v. in the Updates section, p.17, for average annual estimates of imports and BSE release based on current (May 2007) import projections. Based on the BBC prevalence estimate, this table shows an annual average of 0.89 imported infected cattle.

[25] The updated (2007) projections (see Updates section, pp.13-16) show a proportional and absolute drop (relative to the projections published in the original risk assessment) in the number of older cull cattle in the first few years of the 20-year period of analysis. Consequently, an even greater proportion of imports than initially estimated is expected to be less than two years of age.

Like the evidence described in the preceding paragraph, this information is considered in the qualitative evaluations, but not in the quantitative evaluations.

Table 7 below presents projected percentages, total (number) and infected cattle imports by usage type from Canada for 2007, based on estimates of August 2006 prevalence. These values are presented not as estimates of predicted release, but to reasonably inform the quantitative exposure simulations in Section IV of this document.

Table 7. Projected percentages, total (number), and infected cattle imports by usage type from Canada for 2007.[‡] The two prevalence estimates reflect the two methods used in Section III.A.

	Percentages		Number imported 2007	Number infected 2007	
	Sub-group	Overall		Prevalence= $6.8*10^{-7}$	Prevalence= $3.9*10^{-6}$
Slaughter cattle		82	1,121,000	0.76	4.37
Steers/heifers	53.2		728,000	0.50	2.84
Cows	21.1		289,000	0.20	1.13
Bulls and stags	3.9		54,000	0.04	0.21
Calves	3.7		51,000	0.03	0.20
Stockers/feeders		13.8	196,000	0.13	0.76
Breeding cattle		4.2	60,000	0.04	0.23
Dairy heifers/cows	3.6		51,000	0.03	0.20
Beef heifers/cows	0.4		5,000	0.00	0.02
Bulls	0.2		3,000	0.00	0.01
Total	100	100		0.94	5.37

[‡] Updated projections are presented in Table v in the Updates section, page 17. Our original conclusions regarding the likelihood of release of BSE are not sensitive to these data updates.

III.D.1.a. *Release of BSE via import of live bison*

Although the bulk of the live bovines projected to enter the United States following implementation of the amended regulation would be cattle, we also predict the entry of some bison. These animals will also be required to be born after the date of the effective feed ban. Based on 2006 projections, reported in Section III.C, except for the first two years, we predict approximately 2,500 bison to enter annually. In the absence of evidence to the contrary, we assume that the prevalence of BSE in bison is the same as that in cattle. Since no cases have been reported in North American bison, this assumption likely overestimates the BSE risk (the likelihood of establishment and the impact of any cases that may occur even without establishment) associated with importation of this species. Nonetheless, even when assuming that bison are as likely as cattle to be infected with BSE, and when using August 2006 BSE prevalence estimates, we would expect only 0.0098 infected bison imported annually, or one in 103 years, when not considering the additional evidence of the expected impact of a feed ban,

currently, or in the future. Even for 2007, the year in which the greatest number of bison exports was expected (4000), we calculate only 0.0156 infected bison to be imported.

Given that the feed ban applies to all ruminants, including bison, we expect that it has reduced the prevalence in that population as much as it has in cattle. When incorporating the additional evidence from the UK on the expected impact of a feed ban into the August 2006 prevalence estimate, and assuming 2500 animals imported per year, the "expected" number of infected bison drops to 0.0017 per year, or one in 588 years, even when assuming no subsequent drop in prevalence over that period. Given the essentially negligible rate at which we might, even with cautious assumptions, release BSE into the United States via imported bison from Canada, we have elected not to analyze this pathway further.

III.D.2. Release of BSE via import of blood and blood products

As demonstrated in Sections III.A. and III.B.2., multiple steps in the risk pathway act as safeguards against the release of BSE infectivity from Canada into the United States via imported blood and blood products. First, as described in Section III.A., the underlying BSE prevalence in Canada is now extremely low (less than 7 per 10 million cattle under the BBC model, or less than 4 per million under BSurvE Prevalence B), and is expected to decrease further. Therefore, the chance of collecting blood from an infected animal is very small. Even if one of the very few infected animals were a source of imported blood or blood products, several steps, or nodes, in the risk pathway act to further diminish the likelihood of release. The first of these is the evidence that, even in infected animals, BSE infectivity has not been detected in the blood of cattle. Furthermore, the most commonly imported blood-derived commodity, fetal bovine serum, passes through two additional risk-reducing nodes: the very low likelihood of maternal transmission and, once again, the evidence that BSE does not localize to bovine (in this case, fetal) blood.

Additional nodes that apply to both adult- and fetal-derived blood reflect the continued drop in likelihood attributable to blood fractionation. Specifically, even in those species in which any TSE infectivity has been found in whole blood, it is typically at a much lower level in the plasma or serum from which the vast majority of blood-derived commodities are derived. Therefore, even if bovines were to have some infectivity in their blood, it would not persist in the significantly traded commodities (e.g., FBS and BSA).

The pathways described in the previous paragraphs reflect a series of sequential, and hence, multiplicative nodes. The likelihood of infectivity being released directly (not secondary to cross-contamination) via imported blood and blood products is the conceptual product of the likelihoods of each node contained within the pathway. Thus, the product of each of these very low likelihoods yields a negligible likelihood of BSE release via this direct pathway.

III.D.2.a. *Likelihood of cross-contamination at slaughter*

The possibility of cross-contamination at slaughter of bovine blood with infectivity from high risk tissues is an additional potential risk pathway that must be considered. Because this pathway is separate, in part, from the one described above, its effects are additive. Cross-contamination could potentially occur if, during slaughter or processing, collected blood were contaminated with specified risk materials (SRMs). Like the pathway described in the preceding paragraph, the cross-contamination pathway would also be greatly reduced by the very low prevalence of BSE in Canada. However, the cross-contamination risk pathway could bypass the sequential safeguards described above. Existing prohibitions on compressed air stunning will prevent the creation of brain tissue emboli that could potentially contaminate the blood (CFIA 2006a). In order to further minimize the likelihood of release associated with this pathway, we are proposing mitigations that will effectively prevent cross-contamination during the collection process. Specifically, the slaughtered animal (in some cases, the dam of the animal from which the fetal blood is collected) must pass ante-mortem inspection, the uterus must be removed intact and taken to a separate area, and blood (both fetal and non-fetal) must be collected in a closed system.

Based on the evidence and the proposed mitigations described in this document, we conclude that there is a negligible likelihood of BSE release into the United States via blood and blood products imported from Canada.

III.D.3. Release of BSE via import of small intestines other than distal ileum

As for the two groups of commodities described above, live animals and blood and blood products, the likelihood of release of infectivity via imported small intestine from Canada is reduced in large part by the very low BSE prevalence demonstrated in Section III.A. Based on the discussions in Section III.A. and in the introduction to this release summary, we conclude that the current prevalence in Canada will decrease further. If, despite this presumably decreasing prevalence, an infected animal were slaughtered, two additional risk pathway nodes further reduce the likelihood of BSE release via the import of bovine small intestine other than the distal ileum.

The first of these nodes is the likelihood that BSE infectivity would be present in the small intestine, other than the distal ileum. Section III.B.3. presents abundant evidence that such a likelihood is exceedingly small. In essence, all research indicates that when BSE is localized to the small intestine, it is detected only in the distal ileum. All other portions are considered to be free of infectious levels of the agent.

The second node, in parallel, and thus additive in nature to the first, addresses the exclusion of the potentially infectious distal ileum. In Section II.B.3., we discuss the mitigations which require the removal of this SRM. FSIS and FDA have determined that the distal ileum can be effectively removed by discarding the most distal 80 inches of the uncoiled and trimmed small intestine. Their conclusions are supported by anatomic

evidence that the bovine ileum is only two to three feet long (NANCA 2004). Moreover, FDA and FSIS both conclude that small intestine from which the distal ileum has been so removed can be used for human consumption. An authorized veterinary official of the government of Canada will be required to certify that any product containing bovine small intestine adheres to these requirements.

Therefore, the two crucial nodes in the potential risk pathway associated with importation of small intestine other than distal ileum that reduce the likelihood of infectivity are the absence of infectivity in these tissues, and mitigations to ensure adequate removal of potentially infective distal ileum. Based on the presented evidence, we conclude that the likelihood of BSE release via bovine small intestine other than distal ileum imported from Canada is negligible.

III.D.4. Release conclusions

In summary, based on the evidence and proposed mitigations discussed in the release assessment, we conclude that the likelihood of releasing BSE into the United States from Canada via importation of blood and blood products or intestines is negligible. We also conclude that the likelihood of release via live animal imports is extremely low. We note that the numeric estimates presented above are used as inputs for the exposure model discussed in the next section of the document, and do not in themselves represent our expectation of release. Finally, we conclude that the overall likelihood of BSE release via importation from Canada of all of the commodities considered, is extremely low.

IV. Exposure Assessment

IV. A. *Live Bovines*

This section of the risk assessment evaluates the pathways by which infected Canadian cattle, if imported, might expose U.S. cattle to BSE, and the likelihood that these pathways might lead to the establishment of the disease in the U.S. cattle population. The nature and likelihood of these pathways depend in large part on mitigations acting in series and in parallel which reduce the likelihood that BSE will be established in the United States. Although the bulk of this portion of the analysis reflects factors intrinsic to the United States cattle industry, some of the inputs are derived from the preceding release assessment.

As demonstrated in the release assessment, we conclude that the prevalence of BSE among Canadian cattle is extremely low. The models which we used to evaluate prevalence produce two estimates of prevalence for August 2006: one that does not include additional evidence from the UK on the expected impact of a feed ban (BSurvE Prevalence B), and one that does (BBC). We maintain that the latter estimate is more appropriate for this risk assessment because the proposed mitigation requiring that all imported live bovines are born on or after March 1, 1999, means that these animals are subject to the implemented feed ban. In order to determine the significance of this

assertion, we include the higher prevalence estimate in the sensitivity analysis discussed below.

As described in Section III.A.2.a of the Release assessment, empirical observation and simulation studies document a continued drop in prevalence following implementation of a feed ban. Because the rate at which this drop may occur in Canada cannot be adequately quantified, we assume for the purposes of performing a quantitative analysis that prevalence (and thus the likelihood of release) will remain constant over the 20 years of the analysis (2007-2026). Therefore, the numeric outputs presented in this section reflect this more cautious assumption. Our interpretation of these results, however, is further informed by evidence that the prevalence will decrease over this time period.

IV.A.1. Pathway Analysis: Barriers to BSE transmission and amplification

If an infected animal were to be imported, then each of the remaining barriers outlined here would reduce the level of available infectivity in the system. For an infected imported Canadian animal to transmit infection to a U.S. cow, four sets of barriers must be crossed:

1. Slaughter controls and dead animal disposal
2. Rendering inactivation
3. Feed manufacturing and use controls
4. Biologic limitations to susceptibility

Current FSIS slaughter restrictions in the United States decrease the likelihood that any infectious raw materials from an infected imported animal will be incorporated into the human or animal food supply. These restrictions include ante-mortem inspections at the slaughter plant. BSE-infected cattle in the end-stages of infection, and containing the greatest amount of infectivity, will typically present with central nervous system signs or as downer cattle and will be condemned. Prohibiting the slaughter of downer cattle and those otherwise displaying clinical signs recognized as consistent with BSE infection explicitly eliminates the potential for their infectivity reaching humans. Such a condemnation will also trigger a diagnostic investigation of the suspect animal, including a test for BSE. If positive, its infectivity will be inactivated by incineration. Also, without slaughter as an option for handling downer cattle, some farmers and ranchers may dispose of such cattle on their premises, thereby eliminating these cattle as a source of infectivity in cattle feed. Therefore, ante-mortem inspection and the prohibition of slaughtering downer cattle likely diverts material from some infected animals away from the rendering pathway.

The FDA's 1997 ruminant feed ban, found in Title 21 of the *Code of Federal Regulations* Part 589.2000 (FDA 2006) regulates rendering, feed manufacture and use of prohibited feeds to reduce the likelihood of BSE recycling in the United States. Rendering processes in the United States will inactivate significant levels of the agent, further reducing the level of infectivity in prohibited bovine MBM. These processes inactivate much of any potentially remaining infectivity by subjecting the material to intense heat and pressure. Furthermore, federal regulations require that bovine material sent to a

rendering facility must be kept separately from low risk material and must be correctly labeled for use by feed processors. These requirements reduce the likelihood of cross-contamination and mislabeling by renderers.

If a fraction of the hypothetical BSE infectivity were to escape destruction at the rendering facility, it would need to by-pass controls imposed to prevent cross-contamination and ensure proper labeling of rendered materials (at the renderer) and feeds produced using prohibited MBM (at the feed mill). The controls preventing cross-contamination and mislabeling act in parallel to one another and are additive in their risk reduction effects. Proper separation of infectivity by prevention of cross-contamination and mislabeling, act in series with risk reduction steps occurring up to and including rendering. Therefore, controls preventing cross-contamination and mislabeling are multiplicative with these earlier steps in their risk-reduction effects.

The likelihood of exposure to any infectivity remaining in properly manufactured and labeled, but prohibited feed, is reduced by the ban on misfeeding of these feeds to ruminants. However, even if some remaining infectivity were fed to cattle, in order for disease transmission to occur, an individual animal must consume a dose high enough to be infectious given that animal's age-specific susceptibility distribution. In other words, the amount of infectivity present must be adequate to infect an animal ingesting that feed. If the dose is too low, exposure will likely not result in infection. Epidemiological and simulation studies indicate that animals are most susceptible before 4 months of age (Wilesmith, et al. 1988; 1992; 1992a; Ferguson, et al. 1997; De Koeijer, et al. 2004).

Moreover, in the extremely unlikely event that an animal should become infected from contaminated feed, it is unlikely that infectious levels of the agent from that animal would be transmitted to other cattle because infectivity from that animal must also circumvent all of the barriers discussed.

IV.A.2. Quantitative evaluation of BSE exposure and spread in the United States

APHIS has arranged for the primary author of the Harvard BSE model to simulate the impact of the mitigations described above on the likelihood of exposure, establishment and spread of the BSE agent in the United States following the release of infectivity in live animals imported from Canada (see Attachment 2). Therefore, the current BSE simulation model is a revision of one developed jointly at Tuskegee University and at the Harvard Center for Risk Analysis (Cohen, et al. 2001; 2003).

Simulation description modified from Cohen, et al. 2003

The simulation model can be thought of as consisting of four components. The first component characterizes the lifecycle of cattle in the US, quantifies the potential infection of animals at different points during this cycle, and characterizes their ultimate disposition (slaughter, death due to natural causes followed by either disposal or rendering, and death due to BSE infection followed by either disposal or rendering). The second component of the model describes how animals sent to slaughter are processed. Tissue may be disposed of, sent to rendering, or prepared for potential human consumption. The third component of the model characterizes the disposition of material sent to rendering. That material may exit the system (*e.g.*, because it will be disposed of, exported, or used to produce feed for animals other than cattle) or end up in feed that is administered to cattle. In this way, the model keeps track of the extent to which BSE might spread to additional cattle in the U.S., expressed both in terms of additional BSE-infected cattle, and in terms of the disease's reproductive rate, R_0. This information is the focus of the APHIS analysis. The final component of the model quantifies infectivity in material presented for human consumption.

IV.A.2.a. *Methodology*

Historically, the Harvard BSE model (Cohen, et al. 2001; 2003) has been used to evaluate the impact of various alternatives scenarios and risk management options on the possible spread of BSE within the U.S. cattle herd and the potential for human exposure to the BSE agent. The model simulates what might happen if BSE were released into the U.S. cattle population. In doing so, the model estimates whether BSE would develop into a self-sustaining epidemic if it were released into the United States, or if its prevalence would tend to decrease over time, leading eventually to its eradication. Our use of the model focuses on the dynamics of the disease in cattle, rather than possible human exposure.

The probability that BSE could be perpetuated in the U.S. cattle population depends on the average number of new cases of disease that result from each existing case. This value, designated R_0, is referred to as the epidemic's basic reproduction rate (Anderson 1991). If R_0 exceeds unity (one), the disease will tend to spread. Conversely, if R_0 is less than unity, the number of cases will tend to decline over time, and ultimately the disease will die out.

Previous versions and updates reflecting new domestic regulations include parameters likely to influence the predicted spread of the disease. Briefly, these input parameters address:

- Dynamics of U.S. cattle population

- BSE related mitigations during slaughter, rendering and feed production and usage
- The degree of compliance with restrictions on animal slaughter, rendering and feed practices
- The amount of infectivity being carried by an infected animal in different tissues at different times of the incubation period
- Inherent characteristics of cattle, such as age-related susceptibility

IV.A.2.a.1. *Current (2006) updates to the BSE Exposure Model and input parameters*

In order to evaluate the effects of importing cattle born on or after March 1, 1999, from Canada and to incorporate newly available evidence, the author has modified the model in the following ways:

- Cohen, et al. (2001; 2003) evaluated a single importation of infected cattle introduced at the beginning of the simulation. The current revision allows for repeated importations of infected cattle and specification of the age at import, sex, animal type (dairy, beef slaughter, or reproductive beef), age at infection, and expected slaughter age.
- Explicit modeling of potential cattle exposure to the BSE agent via administration of poultry litter in cattle feed. The simulation model incorporates the proportion of prohibited MBM used in poultry feed (separate values are specified for dead and healthy slaughter cattle), and the proportion of poultry litter that is administered intentionally as cattle feed (Attachment 2, Section 2.1.8).

The current version of the model also incorporates updated parameter estimates:

- Efficacy of SRM removal at slaughter
- Proportion of animals that are rendered
- Mislabeling and cross-contamination at rendering
- Mislabeling and cross-contamination at feed mills
- Disposition of MBM
- Pessimistic value of misfeeding for sensitivity analysis

These parameters are described in the following sections along with parameter updates employed in Cohen and Gray 2005, and other significant, although unchanged parameters. In order to be consistent with its historic use in the Harvard model and in Attachment 2, we use the term "pessimistic values" in this context to refer to the plausible higher values used in the sensitivity analysis.

IV.A.2.a.2. *Significant and/or updated (2005-2006) parameters*

The following discussion enumerates and provides the rationale for changes in the input parameters most relevant to our analysis. These changes are consistent with new BSE mitigations, compliance data, and new data on key parameters known to influence the spread of the disease. They include relevant changes made in a recent update of the

model performed for USDA FSIS (Cohen and Gray 2005), and new changes implemented specifically to inform the current risk assessment.

In addition to revisions in the model and its parameters, we also discuss the most important nodes in the risk pathway. Other nodes that have not been deemed to be epidemiologically important (such as maternal transmission or the feeding of plate waste or tallow to cattle) are addressed in earlier publications (Cohen, et al. 2001; 2003) and are not revisited here.

IV.A.2.a.2.(a) Import of infected cattle

As described in the release assessment, the numeric representations of the number of infected cattle entering the United States are based on (1) August 2006 estimates of the BSE prevalence in Canada (Section III.A. and Attachment 1), and (2) the number of cattle we expect to import over the 20 years of the analysis (Section III.C.). Table 7 (Section III.D.) shows the estimates for the number of infected animals imported by age, sex, and type for the first year in which the proposed rule may be implemented, 2007.

The most likely assumption, which we have not attempted to quantify, is that the prevalence will continuously decrease from the current estimates over the 20-year analysis period. In this assumption, the possible numbers of infected animals imported is highest in the first year following implementation of the rule, and subsequently decreases. This assumption does not provide numeric estimates of the importation of infected animals necessary for simulation in the exposure model. Therefore, the exposure model and its results by necessity include the less likely assumption that Canadian BSE prevalence remains constant through 2026.

Based on these numeric representations of BSE release from Canada, the attached, updated exposure model evaluates the outcome of this release of infectivity assuming BSE prevalence in Canada is 6.8×10^{-7}. This estimate incorporates the UK data on the effect of a feed ban.

Although the release section produces two numeric estimates of BSE prevalence in Canada, the proposed mitigation requiring that all imported live bovines are born on or after March 1, 1999, means that these animals are subject to the feed ban. We therefore focus our discussion of the impacts of the proposed live animal imports on results predicted when assuming that Canada's feed ban has reduced BSE prevalence as effectively as that observed in the UK. We evaluate the impact of relaxing this assumption in the sensitivity analysis, in which we analyze the model's outputs assuming the higher prevalence value (3.9×10^{-6}) which omits the additional UK evidence.

Once infected animals are released into the system, the model evaluates how mitigations during slaughter, rendering, and feed production reduce the amount of infectivity potentially available to be recycled and fed to bovines.

IV.A.2.a.2.(b) Slaughter process

BSE-infected animals showing clinical signs of disease are at the end of the incubation period and therefore carry a high infectivity load (Wells, et al. 1996; 1998). Therefore, identification of high risk animals, including those displaying clinical sign of BSE infection at ante-mortem inspection, reduces the probability that these animals and the large amount of infectivity they may carry will enter the normal slaughtering process. As part of the ante-mortem inspection, FSIS veterinarians routinely condemn animals showing clinical signs of systemic disease, non-ambulatory status and/or exhibiting clinical signs compatible with BSE, including central nervous system impairment. For standard surveillance, a condemnation of an animal exhibiting clinical signs of BSE triggers a diagnostic investigation of the suspect animal, including a test for BSE. If positive the animal is destroyed mainly by incineration.

The scenarios simulated in the attached exposure model (Attachment 2) reflect current mitigation measures related to the disposition of non-ambulatory animals and track the ambulatory status of cattle infected with BSE. Ante-mortem inspection and ambulatory status probabilities are based on Cohen and Gray 2005.

In the event that infected animals pass the ante-mortem inspection, many tissues not used for human consumption, including tonsils and distal ileum of all animals and nervous tissue-derived SRMs of animal over 30 months old, go to rendering. As in earlier versions of the model, the author cites FSIS' statement that SRMs are effectively removed 99 percent of the time (FSIS 2005).

IV.A.2.a.2.(c) Proportion of animals that are rendered

Sick, non-ambulatory and dead animals can either be rendered or disposed of in other ways (e.g., burial on farm and landfill disposal). Disposal other than rendering prevents potential infectivity in non-rendered animals from inadvertently entering cattle feed.

Dead stock that is not disposed of on the farm, animals condemned on ante-mortem inspection at slaughter and non-ambulatory cattle from all types of cattle operations are typically collected by rendering firms. Eastern Research Group, Inc. (ERG 2005) and Informa Economics (Informa 2004) prepared detailed estimates of farm mortalities and materials rendered. Informa (2004) estimates that approximately 35 percent of cattle found dead on farm and downers in the United States are rendered (41.9 percent rendered by volume). In contrast, ERG (2005) using other industry-supplied data estimated that the number of cattle mortalities and downers rendered is 17 percent.

In response to comments on its initial analysis and in recognition of the uncertainty about this parameter, FDA substituted new industry data into the analysis, revising its estimate from 17 to 33 percent with an upper bound of 42 percent (FDA 2005a, page 58588). The current analysis (Attachment 2) assumes the higher value of 42 percent to reflect those cattle dying on farm that are rendered. This parameter value is lower, however, than the 85 percent assumed in previous analyses (Cohen, et al. 2001; 2003).

IV.A.2.a.2.(d) Rendering process

Although rendering of infected bovines can potentially allow BSE infectivity to pass into ruminant feed, several mitigations diminish its likelihood of doing so. FDA's 1997 feed ban (FDA 2006) requires that renderers must (1) keep specific records on the manufacture of rendering products, (2) have processes in place to prevent commingling of ruminant and non-ruminant MBM, and (3) ensure that materials containing prohibited MBM are labeled conspicuously with the statement, "Do not feed to cattle and other ruminants." Furthermore, as discussed below, rendering itself serves as an effective mitigation against the perpetuation of infectivity.

IV.A.2.a.2.(d)i. Inactivation during rendering

Although rendering practices vary among plants, the Harvard model (Cohen, et al. 2001; 2003; Cohen and Gray 2005) cites evidence from industry sources, estimating that 95 percent of ruminant MBM is produced using processes that result in at least one log reduction in BSE infectivity. Specifically, 5 percent of ruminant MBM is rendered using a batch system that reduces infectivity by 3.1 logs; 45 percent of MBM is rendered using a continuous flow system to which fat is added that reduces infectivity by 2 logs; and 45 percent of MBM is rendered using a continuous flow system without fat added that reduces infectivity by 1 log. Only 5 percent of MBM is rendered using a vacuum system that results in no reduction in BSE infectivity. The infectivity reduction by type of rendering system is based on inactivation studies (Taylor, et al. 1995; 1997).

We used this evidence to calculate the expected (average) reduction in infectivity from rendering to be 1.4 logs. Thus, roughly 96 percent ($1-10^{-1.4}$) of BSE infectivity is destroyed during rendering allowing only 4 percent of BSE infectivity to survive the rendering process.

IV.A.2.a.2.(d)ii. Cross-contamination and mislabeling at rendering

The likelihood of cross-contamination and mislabeling at rendering depends in large part on the potential presence of risk materials in the facility. Cohen, et al. (2001; 2003) assume that nearly 50 percent of raw material from ruminants is delivered to rendering plants that process only prohibited material, eliminating the possibility of cross-contamination at the renderer (although mislabeling is still possible). Citing industry sources, the authors also assumed that approximately 5 percent of such high risk material is delivered to rendering plants that process both prohibited and non-prohibited material (so-called mixed rendering plants). In these facilities, both cross-contamination and mislabeling are possible. We assume that no mislabeling or cross-contamination occur at dedicated "non-prohibited" rendering facilities.

In order to estimate mislabeling and contamination probabilities, we rely on data collected by FDA/CVM[26] prior to September 2003. Compared to more recently collected inspection data, these data better detail the nature of the violations discovered, reporting the total number of firms with at least one violation and designating each violation as a case in which: 1) products were not labeled as required, 2) the facility did not have adequate systems to prevent co-mingling, or 3) the facility did not adequately follow record keeping regulations. More recent data report violations only in terms of the type of action indicated – *i.e.*, Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI).[27]

As described in Cohen and Gray 2005, these compliance data indicate that mislabeling was detected in 2.3 percent of inspected renderers and possible commingling (cross-contamination) was detected in 1.8 percent of inspected renderers. The model uses these values to indicate the relative likelihoods of these nodes within the risk pathway. Both of these values reflect decreases from higher estimates based on older compliance data used in earlier versions of the Harvard BSE exposure model. Additional details on these parameter values are in the attached exposure model document (Attachment 2). We note here, however, that the use of these data is likely to produce compliance estimates that are lower than current levels because compliance rates with the FDA regulation improved since 2002. For example, the FDA/CVM update of June 2005 (FDA CVM 2005) indicates that 2 (1.1 percent) out of 176 rendering firms handling prohibited materials were classified as OAI.

IV.A.2.a.2.(e) Disposition of meat and bone meal

The revised BSE exposure model includes updates on the disposition of rendered materials. In previous versions, the authors estimated that 15 to 30 percent of MBM produced in the United States was exported. This percentage dropped substantially in 2004 to 5 percent of production (NRA 2005). In addition, because the current model explicitly addresses the poultry litter pathway, the proportion of MBM destined for poultry feed needed to be specified. To incorporate both of these changes to the model, we assume that 50 percent of prohibited MBM goes to feed mills producing prohibited feeds (excluding poultry feed); 5 percent of prohibited MBM goes to mixed feed mills and the remaining 40 percent goes to poultry feed mills. In addition to the poultry litter

[26] Compliance program implementation details can be found at http://www.fda.gov/cvm/CVM_Updates/BSE0806.htm.

[27] From the FDA CVM Web site (http://www.fda.gov/cvm/CVM_Updates/BSE0806.htm): According to FDA, "An OAI inspection classification occurs when significant objectionable conditions or practices were found and regulatory sanctions are warranted in order to address the establishment's lack of compliance with the regulation. An example of an OAI inspection classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented."

"A VAI inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the Ruminant Feed Ban. These include provisions such as minor recordkeeping."

pathway, ruminant MBM from both dedicated prohibited material renderers and mixed rendering plants that may contain infectivity may be incorporated into ruminant feed if it is mislabeled at the feed mill as non-prohibited feed.

The updated BSE exposure model (Cohen and Gray 2005; Attachment 2) also adjusts for increases in the proportion of exported non-prohibited MBM to 30 percent (NRA 2005). This proportion and those going to other feed mill types are presented in Table 8, along with the respective parameter values used in earlier versions of the model.

Table 8. Differences in the parameter regarding the disposition of MBM used for the Cohen, et al. 2001/2003* and 2005/2006 Risk Assessments

	Prohibited Renderer		**Non-Prohibited Renderer**		**Mixed Renderer**	
	P	**NP**	**P**	**NP**	**P**	**NP**
P Feed Producer (other than poultry feed)	50% (63%)	50% (63%)	NA[(a)]	50% (0%)	50% (63%)	50% (0%)
NP Feed Producer	0% (0)	10% (0)	NA[(a)]	10% (85%)	0% (0%)	10% (85%)
Mixed Feed Producer	5% (5%)	10% (5%)	NA[(a)]	10% (5%)	5% (5%)	10% (5%)
Poultry Feed Producer	40% (NA)[(b)]	0% (NA)[(b)]	NA[(a)]	0% (NA)[(b)]	40% (NA)[(b)]	0% (NA)[(b)]
Out (Unavailable to U.S. Cattle)	15% (32%)	30% (32%)	NA[(a)]	30% (10%)	5% (32%)	30% (10%)

*Values for the Cohen, et al. 2001/2003 risk assessments are in parenthesis
Abbreviations: P – prohibited, NP – non-prohibited, NA – not applicable
(a) We assume no product from a non-prohibited renderer is labeled as prohibited
(b) Poultry feed producer was not modeled in the 2001/2003 Risk Assessments

IV.A.2.a.2.(f) Feed manufacturing process

The FDA's ruminant feed regulations (21 CFR 589.2000) (FDA 2006) prohibit the inclusion of high risk source materials in ruminant food. However, some prohibited MBM might cross-contaminate non-prohibited feed, or prohibited feed may be mislabeled as non-prohibited. Information on mislabeling and contamination during the feed manufacturing process used in Attachment 2 is based on 2002 FDA feed ban compliance data (FDA 2002). These data report that 4 percent of prohibited feed is mislabeled, and 1.9 percent of prohibited feed cross-contaminates non-prohibited feed. These values replace higher, less certain estimates used in earlier versions of the model. Table 2 in Attachment 2 shows the differences in the parameter values associated with the handling of prohibited materials during the feed manufacturing process used for the Cohen, et al. 2001/2003 and the 2006 risk assessments.

Although lower than previous estimates, the values used are still higher than suggested by more recent compliance data. Such data show that from a total of 9,575 inspections of feed mills conducted during the fiscal year 2004 and the first half of the fiscal year 2005, 165 firms (1.7 percent) were identified as firms handling animal feeds containing

prohibited mammalian protein that were not meeting the labeling requirements. In addition, of the 9,575 inspections of feed mills, 41 (0.4 percent) of the inspections identified cross contamination or commingling problems in firms that handle animal feeds containing prohibited mammalian proteins (FDA 2005a). Therefore, as for the rendering data above, we conclude that our higher 2002 estimates over-estimate the amount of cross-contamination and mislabeling that currently occurs in feed mills.

IV.A.2.a.2.(g) On-farm misfeeding

We recognize that even if all of the above safeguards are 100 percent effective in preventing contamination of ruminant feed with potentially infective prohibited material, cattle may be exposed to such materials via misfeeding on the farm. This pathway is in parallel to and therefore additive with those prohibiting cross-contamination and mislabeling of rendered material and feed. However, like cross-contamination and mislabeling, the potential impact of, and mitigations from the prohibition on misfeeding are in series, and hence multiplicative with all of the risk reduction steps occurring up through rendering.

The base case scenario for Cohen, et al. (2001; 2003) assumes that 1.6 percent of correctly labeled prohibited feed is misfed to cattle, with a pessimistic estimate of 30 percent used in the sensitivity analyses. Since the sensitivity analyses have shown that this parameter is very influential, (Cohen, et al. 2001; 2003), the National Grain and Feed Association and the American Feed Industry Association provided new data for the estimates (NGFA and AFIA 2005). Their data indicate that while the original expected value of 1.6 percent is reasonable, the pessimistic value used in the sensitivity analyses should be reduced to 5 percent.

IV.A.2.a.2.(h) Poultry litter exposure pathway

As described in the section on disposition of MBM, current FDA regulations allow the use of ruminant MBM (prohibited MBM) in poultry feed. In the United States, poultry litter can be legally used as a feedstuff for ruminants. Because poultry feed may contain ruminant meat and bone meal which is prohibited in ruminant feed, there is a potential risk that poultry litter may contain spilled poultry feed or potentially intact infectivity excreted in fecal waste. Cattle fed the poultry litter may then be exposed to infected materials. The current assessment incorporates this potential pathway into the larger evaluation of the risk of the importation of infected Canadian cattle. Like misfeeding, the poultry litter pathway is additive to the controls implemented to prevent cross-contamination and mislabeling, and is multiplicative to the controls up to and including rendering.

Poultry litter is a waste by-product of poultry production, containing bedding material, fecal matter, feathers and spilled poultry feed. It is generally only used as cattle feed in particular geographic areas in major broiler producing states where cattle and poultry production enterprises are in close proximity. Since the exposure model simulates the fate of infectivity in the entire U.S. herd, we use information provided by relevant

industry representation (Custer personal communication 2005), estimating that on average, 1 percent of poultry litter nationwide will be used in cattle feed.

We assume that prohibited ruminant protein (and any infectivity which it may contain) is most likely to enter poultry litter via spilled poultry feed. We are uncertain, however, of the proportion of infectivity that enters the litter. We therefore over-estimate this proportion by assuming that 100 percent of any infectivity that may be in poultry feed goes to the litter.

IV.A.2.a.3. *Sensitivity analysis*

The exposure model includes a sensitivity analysis to identify potentially important assumptions. These assumptions were evaluated by holding all but one set of assumptions equal to their base case values. The set of assumptions were set to pessimistic values to see if doing so influences key model predictions – in particular, for this analysis, the predicted number of cattle infected with BSE in the United States over a 20 year period. In addition to determining if the parameters impact the outputs, the sensitivity analysis also provides a ranking of the parameters with respect to the relative magnitude of their effects.

The parameters analyzed include four "endogenous" factors inherent to the U.S. system that influence the fate of released infectivity, and one "exogenous" factor, external to the system, that influences the amount of infectivity released. The endogenous parameters assessed in the sensitivity analysis are:

(1) Mislabeling and contamination – We have revised the base case values for these parameters to take into account new data on compliance rates. The sensitivity analysis evaluates the impact of these revisions by using the previous base case values from Cohen, et al.'s 2003 report as the pessimistic values in the current analysis. In particular, for the sensitivity analysis we increase the mislabeling rates to 5 percent for both MBM and feed production. We increase contamination rates to 14 percent for MBM production, and 16 percent for feed production (Attachment 2 Section 2.2.4).

(2) Misfeeding – The base case value for this parameter is 1.6 percent. We investigate the impact of using the pessimistic value of 5 percent for this parameter (Attachment 2 Section 2.2.9).

(3) The render reduction factor – We change the distribution of render reduction factors using the worst case assumptions for this parameter from Cohen et al.'s October 2003 report.

(4) The proportion of poultry litter used in cattle feed - The base case value for this parameter is 1 percent. The sensitivity analysis investigates use of 5 percent for this parameter.

The exogenous parameter assessed in the sensitivity analysis is:

> (5) Importation of infected animals as a function of Canadian prevalence estimate – Using the BSurvE method described in Section III.A. we can assess the impact of imports from Canada assuming a higher Canadian BSE prevalence estimate. In particular, omitting the additional information on the impact of the UK feed ban from the calculation provides a BSE prevalence estimate for Canada of approximately 3.9 x 10^{-6}, nearly six times higher than the base case prevalence (6.8 x 10^{-7}) which includes the assumption of the impact of a feed ban.

In the final sensitivity analysis scenario, all five uncertain parameters were simultaneously set to their pessimistic levels. Doing so allows us to explore the impact of this unlikely, but possible situation.

IV.A.2.b. *Results*

IV.A.2.b.1. *Base Case Results*

The following paragraphs summarize the results from the model simulations. As previously noted, the most likely prevalence assumption – the prevalence decreases continuously – was not included in these simulations. Therefore, the base case as described reflects the less likely assumption that the prevalence stays the same for the period of this analysis.

Under base case conditions, our results indicate that the expected (average) number of infected cattle occurring in the United States over 20 years as a result of importing cattle from Canada is 21 animals. Most of these infected animals (90 percent) would be imported directly, while the remaining 10 percent (approximately 2 animals) would represent secondary infections (i.e., native U.S. cases). Of the 21 in the United States, 0.67 animals would survive to show clinical signs (Attachment 2, Appendix 2A). The expected value of the reproductive constant for BSE (R_0) is far less than 1 (0.04), indicating no possibility of establishment of BSE in the United States as a result of the release of potential infectivity from Canada.

We are 95 percent confident that at base case levels, the total number of infected animals in the United States over 20 years of the analysis will not exceed 30 animals. We are also 95 percent confident that there will be 24 or fewer animals imported and six or fewer native U.S. cases (Attachment 2, Appendix 2A). In addition, we are 95 percent confident that under base case assumptions, R_0 will not exceed 0.25.

IV.A.2.b.2. *Sensitivity Analysis Results*

The sensitivity analysis indicates that, of the endogenous parameters, the most important sources of uncertainty are the misfeeding rate and the extent to which poultry litter is used in cattle feed (Attachment 2).

The exogenous source of uncertainty, the prevalence estimate with its resulting release of infected animals, is the most important source of uncertainty. The higher value used in the sensitivity analysis is 5.7 times greater than that used in the base case. Not surprisingly, the number of imported infected animals (108) and the number of new cases (12) are 5.7 times greater than those expected in the base case. The R_0 value of 0.075 is only slightly higher than that at the base case (0.04), reflecting that the U.S. system is essentially unchanged by additional released infectivity.

When using pessimistic values for all five uncertain parameters analyzed, the average number of total infected cattle (including imports) over the 20 years of the analysis is 150. Of these, 42 are U.S. born animals and less than 8 survive long enough to develop clinical signs. Furthermore, in this highly unlikely scenario, the reproductive constant, R_0, remains consistently less than 1, with an expected value of 0.23 (Attachment 2, Appendix 2A). That is, even under the worst set of assumptions considered here, BSE infectivity released via live animals from Canada will not establish, and will instead disappear from the population.

IV.A.3. Live animal qualitative exposure assessment

As discussed in the release section (Section III.D.), evidence indicates that implementation of a ruminant feed ban results in decreasing BSE prevalence over time. Therefore, in the most likely scenario, prevalence will decrease in Canada over the next 20 years. In addition, the proposed mitigation (imported animals must be born on or after March 1, 1999) would ensure that imported animals are less likely to have been exposed to the BSE agent. Finally, based on ERS projections, the majority of imports are expected to be less than two years of age at the time of import. For example, approximately 75 percent of animals imported in 2007 would have been born in 2005 or later (Table 4). As the 20-year time frame for the analysis proceeds, so would the downward pressure on the prevalence rate and the amount of circulating infectivity. This leads to a continuously decreasing possibility that animals would be exposed to BSE. However, without a quantitative estimate for the precise rate at which Canada's BSE prevalence may fall, we cannot produce numeric values that accurately represent this scenario.

In addition, the import projections indicate that a higher number of imports would be expected in during the first year of implementation (in our analysis, this was 2007). When this projection is combined with the BBC prevalence estimate – determined to be more applicable to the amended regulation – less than one infected animal would be expected to be imported that year. With the expectation that the prevalence would decrease, and the mitigative effects of both the import requirements and the young age of animals at the time of import, the highest likelihood of release would be in first year of implementation. Qualitatively, we would therefore expect that over the 20 years of the analysis, prevalence, release, and hence, the number of infected animals occurring in the United States as a result of exposure, would be lower than indicated by the results of the quantitative model.

IV.A.4. Live animal exposure summary

In summary, if infectivity at the levels analyzed, either quantitatively or qualitatively, were released into the United States from Canada, then biological factors (e.g., age-dependent susceptibility), and mitigations reducing the likelihood of transmission at slaughter, rendering and feed manufacturing and use would prevent BSE amplification in the United States. Furthermore, the quantitative model produces estimates of the reproductive constant, R_0, that predict that any imported infectivity will ultimately disappear from the population.

IV.B. *Qualitative exposure assessment for blood and blood products imported from Canada*

In the release assessment, we presented evidence that bovine blood and blood products from Canada are highly unlikely to carry BSE infectivity into the United States. In this section, we assess the likelihood of exposure to infectivity if, despite the evidence, such commodities were indeed contaminated with the BSE agent. Because the primary blood products imported into the United States for use in manufacture of veterinary biologics and drugs are fetal bovine serum (FBS) and bovine serum albumin (BSA), we focus our analysis on the potential exposure pathways associated with those products.

The pathways under consideration are those which might allow potential BSE infectivity in imported FBS and BSA to persist through the steps in the manufacture of animal biologics and pharmaceuticals, and result in cattle exposure to, and subsequent infection with BSE. As explained in Section III.B.2, we utilize TSE studies on other species because no comparable work can be done on BSE in cattle blood, given that it has never been detected.

IV.B.1. Risk mitigation by processing of FBS and other blood products

Extrapolating from studies in other species, we expect that some of the processing steps used in preparation of FBS and BSA and the products derived from them further reduce the likelihood of BSE transmission. Those steps which may result in mitigation of BSE risk by removal through separation techniques, potential inactivation through gamma irradiation, and dilution, are discussed here.

Several reasons have been given for the marked decrease in TSE infectivity during these separation processes. The pathogenic conformation of the prion protein (PrPSc) has a low solubility in aqueous solution, forms aggregates readily, and has an affinity for adhering to surfaces (Foster 1999). These attributes contribute to the reduction of the likelihood of BSE transmission via FBS and BSA through centrifugation and filtration (Foster 2004), processes which are used in the preparation of FBS and plasma fractions and in the collection of cell culture products for use as biologics or in the manufacture of pharmaceuticals.

Plasma, serum and other derivatives are obtained from various processes applied to whole blood. Serum is derived from whole blood through the following process. Whole blood is collected into sterile blood bags and is allowed to clot. The clotted blood is centrifuged for removal of the clot and separation of serum from the blood cells. This initial separation step has been demonstrated to remove TSE infectivity from other species' serum fraction (Brown, et al. 1998; 1999; Houston, et al. 2000; Hunter, et al. 2002). The resulting serum may include nutrient proteins, growth factors, hormones, lipids, minerals, and metabolites necessary for cell culture. The serum is decanted, prefiltered, pooled with a variable number of other animals' serum, sterile filtered, and frozen. Because of the properties described in the preceding paragraph, the decanting and filtration steps would further remove any infectivity that might possibly have remained in the serum. Furthermore, the pooling step would dilute any single donation from a subclinical case of BSE.

Pooled FBS is subjected to filtration using 0.1-0.2 micron filters and, for cell culture applications, irradiated to mitigate the likelihood of potential contamination by bacterial and viral agents. According to APHIS Center for Veterinary Biologics records, gamma irradiation is applied commercially at c. 25-50 kiloGray (2.5-5 megaRad) prior to its use in vaccine production. Most commercially applied mitigations are appropriate for prevention of bacterial and viral disease transmission via blood-derived biologics. TSE infectivity, however, is in general highly resistant to conventional inactivation techniques (Taylor 2003).

Unlike heating and other standard steps to ensure freedom from microbial contaminants, gamma irradiation may reduce BSE infectivity. Miekka, et al. 2003 demonstrated that scrapie was inactivated by an estimated 1.5 $\log_{10}$ in human albumin 25 percent solution, using 50 kGy, while causing only moderate alterations to the albumin. We do not, however, have direct evidence for the efficacy of gamma irradiation as a BSE mitigation in bovine blood products. Thus, although we may speculate that slightly lower levels of gamma irradiation used to prevent the transmission of viruses in commercially processed bovine sera may have some mitigative effects on levels of BSE infectivity, we have no direct evidence of such.

To prepare plasma products from whole blood, anticoagulants such as sodium citrate or EDTA are added to the collection receptacle to prevent clotting. This blood, collected generally from live adult bovines, is then centrifuged and filtered. Using fractionation techniques such as cryoprecipitation, centrifugation and filtration, plasma is commercially separated into various components, among which are Fraction II containing immunoglobulins and Fraction V containing albumin (BSA) (Comer 2004, p. II.23). In experimental rodent models, several studies have shown that the very low level of plasma infectivity is dramatically reduced during this fractionation process (Brown 2001). It has been observed that discarding of Fraction III and Fraction IV from immunoglobulin and from albumin, respectively, results in further TSE removal for various strains (scrapie, BSE, CJD) in rodent models (Foster 2004). Separation is achieved by removal of the precipitate. The supernatant and sometimes a redissolved precipitate are then commonly clarified by further filtration. Because of the BSE agent's properties described above,

these additional separation steps would further reduce the likelihood of BSE transmission. The overall process reduction factors for TSE infectivity of the various plasma proteins have been estimated to be quite large. For example, the infectivity reduction factor is 10^{13} for albumin and 10^{9} for immunoglobulins (Foster 1999).

Although whole blood or buffy coat transfusion has resulted in experimental transmission of BSE or scrapie between sheep (Hunter, et al. 2002), and in iatrogenic transmission of vCJD between persons in the UK (Farshid, et al. 2005), transmission by other blood products has not been demonstrated in natural animal hosts of TSEs nor in natural infection of animals or humans (Brown 2001). No transmissions of vCJD have been attributed to plasma derivatives, even among such groups as hemophiliacs that must often use these products (Taylor 2003; WHO 2003). We infer that these observations may result from the reduction in TSE infectivity due to the fractionation processes used in the preparation of these products.

IV.B.2. FBS and blood product use in veterinary vaccine and drug manufacture

FBS is used as a nutrient in cell culture growth media during production of viral vaccines and to propagate difficult-to-grow microorganisms. The basic steps for production of veterinary vaccines are equivalent to those used in the production of human vaccines (FDA 2001). Both often require FBS and sometimes BSA, used as growth media or as stabilizers in a number of biological products, supporting bacterial growth and cell cultures that propagate virus.

The cell lines used in vaccine production are not permissive for prion replication (Harris 1999; Solassol, et al. 2003), so there is no opportunity for amplification of possible TSE contamination. The vaccine virus is grown and harvested from the cell culture, and largely separated from the cell supernatant containing the FBS. There may be trace amounts of FBS remaining in the viral pellet, but this represents a minute amount of the final vaccine dose. Thus, even if BSE-infected FBS were used in bovine vaccine production, the FBS itself does not remain in the final product in amounts adequate to result in infection.

The evidence presented here demonstrates the sequential barriers to exposure to BSE infectivity from blood and blood products imported from Canada:

1. prion protein has a low aqueous solubility, readily forms aggregates and adheres to surfaces, reducing the likelihood of it persisting through the various separation and filtration steps throughout the FBS and vaccine manufacture process;
2. blood products such as BSA pass fractionation steps that further reduce the likelihood of BSE being transmitted;
3. the additional steps in the manufacture of vaccines and other products serve to separate potential infectivity from the processed product.

This evidence is further supported by the absence of an epidemiologic link between vaccine administration and clinical cases of BSE in cattle (WHO 2003). Therefore, despite the uncertainties of applying data collected on other TSEs and host species, the strength of

the evidence that we have collected allows us to conclude with adequate certainty that even if BSE were present in bovine blood products collected in Canada, the likelihood of exposure of animals in the United States to such infectivity is negligible.

IV.C. *Qualitative analysis for exposure resulting from the importation of small intestine other than the distal ileum*

In the preceding release assessment, we demonstrate that the likelihood of entry of BSE infectivity in imported of bovine intestine from Canada is extremely low. In this section, we evaluate the pathways by which BSE infectivity could potentially expose U.S. cattle, if despite our earlier findings it were released in imported bovine small intestine other than the distal ileum. We also assess the likelihood that these pathways might lead to exposure that could potentially cause animal disease and the establishment of BSE in the U.S. cattle population.

As described in Section IV.A., the feeding to ruminants of ruminant protein is expressly prohibited by FDA (21 CFR 589.2000, FDA 2006). This feed ban applies to both non-edible intestine, as well as that intended for human consumption. Therefore, exposure of cattle to BSE infectivity assumes subsequent misdirection, mislabeling, misfeeding, or cross-contamination in feed processing. As demonstrated in the quantitative exposure assessment for imported live bovines, spread via these various pathways is extremely rare, even when considering importation of entire animals. We infer, therefore, that imported Canadian bovine intestine is highly unlikely to be fed to U.S. cattle, or lead to spread of BSE.

We recognize that some small fraction of imported bovine small intestines, inspected and prepared for human consumption, may be legally offered per FDA's "plate waste" exemption[28]. However, very few firms are processing human waste food for ruminant consumption (Pritchett 2004 personal communication). Furthermore, since FDA requires that the plate waste be further heat processed for feed, it may be subject to rendering processes that can inactivate the agent, further reducing the level of infectivity in MBM (Cohen, et al. 2001; 2003).

Despite the uncertainties associated with the precise likelihood of cattle consuming imported bovine small intestines from Canada, given the available evidence, we conclude that exposure of U.S. cattle to BSE in bovine small intestine imported from Canada is extremely unlikely. Therefore, the likelihood of infection and subsequent establishment of the disease in the U.S. cattle population is negligible.

V. Consequence Assessment

In accordance with OIE guidelines, the first two sections of this animal import risk assessment examine the likelihood of BSE release and exposure. The consequence assessment is intended to address the impacts expected if, despite the likelihood of

[28] 21 CFR 589.2000 exempts the feeding of "inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste…)."

release and exposure estimated in the preceding sections, new cases of BSE were to occur in the United States. Consequences requiring consideration are economic and environmental. To fulfill obligations under the National Environmental Policy Act (NEPA), impacts to the human environment are addressed in the accompanying environmental assessment. The following discussion addresses the economic impacts that we would expect if additional BSE cases were to result from the proposed regulatory change. Following OIE guidelines, in the risk estimation section we subsequently combine the impacts described in the consequence assessment with the likelihoods described in the release and exposure assessments to evaluate the potential economic impact of BSE associated with the rule.

The economic impact of BSE includes a variety of costs; some are long-term costs that continue regardless of new cases, others are one-time costs associated with new cases. One long-term impact is the potential loss from actions taken by foreign governments to restrict imports of U.S. live bovines, beef and beef products. This impact tends to decline over time as exporting and importing countries find ways to resume mutually beneficial trade while maintaining the safety of the beef supply. International organizations such as OIE have developed international science-based standards to permit safe international trade in beef from countries that have BSE. U.S. producers incur other long-term costs by complying with domestic regulations to protect animal and human health. U.S. producers and processors must comply with a variety of regulations designed to prevent the BSE agent from entering the ruminant feed chain and to prevent potentially infected ruminant tissues from entering the human food chain. U.S. regulations pertaining to SRM removal, restrictions on use of SRMs, and other changes mandated of the beef processing and feed processing sectors are examples of this type of impact. Another long-term cost is that for BSE surveillance which will continue into the foreseeable future.

The impacts of any new BSE cases are confined to the incremental costs associated with those actual cases. These potential impacts are of two types, regulatory costs and domestic market impacts from consumer reaction to additional BSE cases. Based on the U.S. experience with native BSE cases detected, the regulatory costs per case total approximately $250,000 for epidemiological investigations and indemnity costs for animals sacrificed as part of those investigations.

Consumer impacts of new cases

Any evaluation of potential consumer reaction to additional BSE detections must be evaluated in the context of the reliability of past predictions. These predictions have been based on consumers' reactions in other countries, retrospective U.S. surveys of consumers' purchasing habits, and surveys about how U.S. consumers would react to new BSE cases.

Predictions of U.S. consumer reactions to additional BSE cases were often dire. Researchers at North Dakota State University (Jin, et al. 2004) predicted a 20 percent decline in U.S. beef consumption if more BSE cases were found. This report, as well as

others suggesting possible significant declines in U.S. beef consumption, was based in part on the declines in beef consumption observed in countries such as the UK, Japan, and Germany after BSE was detected in those countries. A number of similar articles were published shortly after the initial U.S. BSE detection (December 23, 2003) after cattle prices had fallen dramatically following the official announcement.

As discussed below, these predicted large reductions in beef consumption did not materialize when BSE was detected for the first, second, or third time in the United States. The very limited reaction of U.S. and Canadian consumers to BSE outbreaks in their countries compared to consumer reactions in Japan, UK, and Germany may be due in part to the very different nature of the BSE outbreaks in North America and those in Europe and the United Kingdom. The number of cases identified in North America (three in United States and 10 in Canada since 2003) has been very limited, especially in comparison to the number of cases identified in Europe (over 185,000 in the UK alone). Perhaps more importantly, cultural perceptions, and consumer confidence and trust are different in these countries (Priest, et al. 2003; Moon and Balasubramanian 2001).

Retrospective and prospective surveys of consumer behavior

Kansas State University researchers (Coffey, et al. 2005) reported the results of five surveys in which consumers reported their past and expected beef consumption in response to actual or hypothetical U.S. BSE cases, respectively. The surveys indicated that about 15-30 percent responded that they had reduced beef consumption after the December 2003 BSE case in Washington State. Depending on the number of potential new BSE cases, 32-45 percent of respondents claimed that they would reduce their beef consumption. However, consumer confidence surveys run for the National Cattlemen's Beef Association show a high confidence in the safety of U.S. beef from "mad cow disease," and somewhat paradoxically, this confidence has shown small increases following the announcement of the BSE cases in the United States (NCBA 2005).

These varying results are expressions of consumers' preference to survey questions. A different and likely more informative way of examining consumers' reactions to BSE relies on preferences as revealed by their buying patterns. This revealed preference, described in the following section, does not suffer from the potential biases in survey results.

Analysis of market response

In contrast to surveys that ask consumers to report their purchasing habits and to speculate about how they would react to additional cases of BSE, are empirical studies that examine market effects (changes in quantities purchased and prices paid) of BSE announcements. Those studies reporting actual consumer behavior all indicate that the effect of the BSE announcements on consumer purchases of beef, if any, was small and transitory.

In a USDA-ERS economic chronology of BSE in North America (Mathews, et al. 2006), the authors note that for a variety of reasons the adverse effect of the BSE cases was minimal and short-lived. U.S. consumers did not reduce their consumption of beef after BSE was detected and U.S. retail prices did not decline. In fact, in 2004 U.S. consumers increased beef consumption by 9 percent compared to 2003 and U.S. retail beef prices rose nearly 10 percent, indicating a strong increase in demand for beef, not a decrease. U.S. retail prices rose an additional 5 percent in 2005.

In a separate analysis, USDA-ERS researchers conducted a detailed analysis of market data to determine how BSE announcements affected market behavior and the demand for beef and beef products (Kuchler and Tegene 2006). Their results indicate that most of the observed change in demand for beef following the BSE announcement in 2003 was due to trend, season, and retail prices. In all products examined, food purchasing patterns returned to pre-announcement levels within two weeks. Dahlgren and Fairchild (2002) reported a similar pattern (small and transient effect on consumer demand) in their examination of how news coverage about bacterial contamination in chicken affected U.S. consumer demand for chicken.

The impact of additional BSE cases on U.S. export markets will probably also be minimal. After the first U.S. BSE case was discovered, many of the 114 nations which imported U.S. beef banned our beef and live animals, but over half – including our largest export market, Japan - have resumed importing U.S. beef (USDA 2006).[29] The joint U.S.-Japan press statement for resuming trade in beef and beef products after market closures in response to finding BSE in the United States contained a provision noting "additional BSE cases will not result in market closures and disruption of beef trade patterns without scientific foundations" (USDA 2004).

Thus, we recognize that ongoing costs of BSE prevention will continue even in the absence of future cases. The costs that we may expect to be associated with the investigation of potential future cases are relatively minor. Finally, we do not foresee significant costs due to drops in domestic beef consumption or imposition of additional trade barriers to international export markets.

VI. Risk Estimation

The BSE risk associated with the proposed additional imports of bovine commodities from Minimal Risk Regions (currently, Canada) is the conceptual product of the amount of release that is likely, the likelihood of exposure given that amount of release, and the resulting economic consequences. We define the BSE risk as the likelihood of establishment and the impacts of cases that might occur even without establishment. Potential impacts to the human environment are addressed in the accompanying environmental assessment.

[29] The temporary closure of the U.S. export market to Japan on January 20, 2006, was a response to a specific commodity concern and not to the likelihood of BSE infection in the U.S. herd.

As in the exposure and release assessments, we estimate the BSE risks associated with each of the proposed commodity groups separately. We then combine these respective risks to estimate the cumulative BSE risk of importing the proposed commodities.

VI.A. *Live bovines*

The likelihood of release is extremely low because prevalence is extremely low and mitigation requiring imported animals to be born on or after March 1, 1999, would further decrease the likelihood that those animals had been exposed to infectivity. We expect the prevalence to decrease continuously over the next several years. With this effect, the amount of release, already low, decreases with the decreasing prevalence (until the disease is eradicated). Although this scenario is the most likely, the Bayesian Birth Cohort (BBC) approach as described is surveillance-based and cannot incorporate empirical and simulated evidence to project expected decreases in prevalence levels over time. Therefore, our expectation that prevalence in Canada, and hence release of BSE infectivity will decrease over time, cannot be incorporated into the quantitative model which informs our exposure assessment. Based on the evidence presented in this document, APHIS concludes that the likelihood of BSE release from imported Canadian cattle born on or after March 1, 1999, is extremely low.

Import of bison is allowed in the proposed rule, but would constitute such a small fraction of imports (approximately 0.2 percent in the original analysis), that they are not analyzed separately. [30] We assume that our conclusion that the likelihood of release is extremely low for cattle also applies to bison.

Even though APHIS concludes that decreasing Canadian prevalence is most likely, we quantitatively analyze the impact of the constant BSE prevalence produced by the BBC model to simulate potential BSE exposure in U.S. cattle. This calculation provides a reasonable estimate (and likely an overestimate) of prevalence and subsequent release of infectivity over the 20 years of the analysis. Using the BBC estimate over this timeframe, the model estimates release of approximately 19 infected bovines. As an expression of our uncertainty regarding the application to Canada's prevalence calculation of the additional UK data on the efficacy of a feed ban, we performed a sensitivity analysis which excluded this additional information. That more risk-inflating and less likely scenario results in the importation 108 infected bovines over 20 years.

Qualitatively, the exposure assessment demonstrated that, because we expect Canada's prevalence to decrease over time, and because of the barriers to BSE transmission in the United States, that the likelihood of BSE exposure and establishment in the U.S. cattle population is negligible. Quantitatively, the exposure assessment evaluated the impact of the numbers of infected animals imported using our assumption of constant prevalence, on the likelihood of U.S. cattle exposure to BSE. We based our evaluation on the Harvard Center for Risk Analysis BSE simulation by Cohen et al. (2001; 2003), updated to incorporate new evidence and domestic regulations and the proposed changes

[30] 0.9 percent according to the updated import projections from USDA ERS, as discussed in the Updates section.

considered here. This model indicates that even when assuming no drop in prevalence in imported Canadian cattle and overestimating the potential for BSE to pass various steps in the exposure pathway, there is little spread of disease to U.S. animals. When including these assumptions, the release of approximately 19 imported infected animals, leads to approximately two U.S. cases as secondary spread and 0.67 animals showing clinical signs over the 20 years of the analysis.

The reproductive constant for BSE (R_0) is far less than the value of 1.0 necessary to maintain disease in the U.S. cattle population. Even when higher plausible values were applied for all uncertain parameters evaluated in the sensitivity analysis, R_0 is 0.23, well below 1.0 (Attachment 2, Appendix 2A).

The significance of this R_0 value is magnified by the expectation, despite the assumptions in our models, that BSE infectivity in Canada (and thus released into the United States) is likely to decrease over time. Thus, although the results of the exposure model assume no change in prevalence over time, empirical evidence (DEFRA 2006, EC 2005a) and simulation studies (Cohen, et al. 2001; 2003) suggest that Canada's feed ban will continue to decrease BSE prevalence in that country. Also, several parameters in the base case scenario of the exposure model likely overestimate the likelihood of BSE transmission. Thus, we expect the number of native U.S. cases to be less than those predicted in our analysis.

Considering evidence provided in the consequence assessment (Section V.), we expect that the 0.67 clinical cases that we estimate may occur over 20 years (equivalent to 1 in 30 years) will result in negligible economic costs of BSE. Although clinical cases are the only manifestation of BSE in an animal population, APHIS acknowledges that the possibility of preclinically infected animals is a concern. Thus, although human health is not the focus of this assessment, we note that, even our quantitative model, which includes multiple sources of risk over-estimation, indicates that over the 20 years of the analysis, only 45 cattle oral infectious dose-50 (ID_{50}) units will potentially be available for human exposure. Although this result is discussed in more detail in the accompanying environmental assessment (APHIS 2006), we note here that compared to estimated potential exposure levels in the UK of 54 million cattle oral ID_{50} units over 24 years (Comer and Huntly 2003), this number is insignificant.

VI.B. *Blood and blood products*

In the release assessment we concluded from presented evidence that multiple steps in the risk pathway act as safeguards to prevent release of BSE infectivity from Canada via imported blood and blood products. First, the BSE prevalence in Canada is extremely low. Therefore, the likelihood of collecting blood from an infected animal is small. Even if an infected animal were a source of imported blood or blood products, several steps, or nodes in the risk pathway act to further diminish the likelihood of release. The first is that, even in infected bovines, BSE infectivity has not been detected in blood. Second, the likelihood of cross-contamination at collection is significantly reduced by the

proposed mitigations. We conclude that the likelihood of release of BSE infectivity in bovine blood and blood products is negligible.

In the exposure assessment, we further examine the role of various separation and processing steps in reducing infectivity. We also note the absence of an epidemiological link between administration of vaccines manufactured using tissue culture supported by fetal bovine serum and clinical cases of BSE (WHO 2003). We conclude that the steps in the production and use of products manufactured with bovine blood or its derivatives are likely to further reduce any possible infectivity.

Given that the likelihood of both release of BSE via the importation of bovine blood and blood products from Canada and exposure of bovines to any such introduced infectivity is negligible, we conclude that extremely few or no U.S. cases of BSE would result. Therefore, the BSE risk associated with their importation is negligible, as well.

VI.C. *Bovine small intestine other than the distal ileum*

In the release assessment we present evidence that the small intestine of BSE infected cattle has detectable infectivity only in the distal ileum. Other portions of the small intestine that have been examined do not contain detectable infectivity. We also supply evidence that FSIS' and FDA's regulations ensure adequate removal of the distal ileum, thus effectively mitigating the likelihood of contamination of exported bovine intestines with infectivity from the distal ileum.

In the exposure assessment, we examine possible pathways for bovine exposure to infectivity that may potentially be released from Canada in bovine small intestines other than the distal ileum. We found no epidemiologically significant exposure pathways. Combining these findings, we conclude that the joint likelihood of BSE release and subsequent exposure of bovines to infectivity from imported bovine intestines other than the distal ileum is negligible. We further conclude that this negligible likelihood would result in extremely few or no U.S. cases of BSE. Therefore, the BSE risk associated with the importation of these commodities is negligible.

VI.D. *Conclusion of Risk Estimation for all commodity groups considered*

We conclude that over the 20 years of the analysis, the risk to the United States of BSE - the likelihood of establishment and the potential impacts of cases that may occur even without establishment - as a result of importing the bovine commodities considered here from Canada, is negligible. We base that conclusion on several components of the analysis. The qualitative assessments for blood and blood products and small intestine demonstrate negligible likelihood of both release of, and exposure to, BSE infectivity. The qualitative and quantitative assessments of release of BSE via the import of live bovines from Canada demonstrate an extremely low likelihood of release, and that, because of the comprehensive mitigations already in place in the U.S., the likelihood of establishment is negligible. Even when incorporating risk-inflating assumptions, such as regarding the poultry litter pathway and rates of compliance, the quantitative exposure

assessment demonstrates that very few, if any, U.S. born animals will be infected and that even fewer might develop clinical signs of disease. Economic costs secondary to BSE release into the United States via the importation of these commodities will therefore be negligible.

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Attachment 1: Estimation of BSE Prevalence in Canada

1. Introduction

The purpose of this document is to estimate the prevalence of bovine spongiform encephalopathy (BSE) in the adult cattle population of Canada. The detection of Canada's first native BSE case was confirmed on May 20, 2003. As of August 23, 2006, a total of nine BSE cases of Canadian origin had been confirmed in North America (CFIA 2006). This total includes a case of BSE that was confirmed in Washington State on December 25, 2003. By comparison, the United Kingdom (UK) had detected 184,453 cases of BSE as of September 1, 2006 (OIE 2006a).

The number of BSE cases detected through surveillance understates the disease prevalence because exposed animals may be incubating disease and carrying infectious material in their tissues without presenting clinical symptoms. Like many transmissible spongiform encephalopathies (TSEs), BSE has an incubation period of several years. Therefore, the disease is not detectable in its early stages with current technology. Moreover, surveillance will miss a proportion of detectable cases. Therefore, statistical methods are applied to the available epidemiologic and surveillance data to estimate, with attendant uncertainty, the prevalence of BSE in Canada.

Two related, but distinct methods were used to estimate BSE prevalence in Canada. Given its international prominence, we used the European Union (EU) BSurvE model (Wilesmith *et al*. 2004, 2005), recently developed for the purpose of estimating BSE prevalence in national herds. The BSurvE model is noteworthy for its sound epidemiologic structure, including stratifying cattle by age and cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) and accounting for the relative likelihood of detecting BSE in various strata (EFSA 2004). The primary prevalence estimation method used in this document, referred to as the Bayesian Birth Cohort (BBC) model, takes advantage of the BSurvE model structure to calculate BSE surveillance point values - random sample size equivalents - represented by targeted Canadian sampling of certain groups of cattle in which BSE cases are more likely to be detected. The Bayesian Birth Cohort model adopts a Bayesian statistical framework to incorporate prior information about the decreased incidence of BSE observed in animals born after a feed ban equivalent to the initial ruminant-to-ruminant feed ban introduced in the UK in 1988. For the purposes of comparison and sensitivity analysis, the prevalence of BSE in Canada also is estimated using BSurvE.

2. Data

2.1 BSurvE Model Structure for Input Data

Applying the BSurvE model structure to estimate a country's BSE prevalence requires knowledge of the cattle population size and age structure and involves important assumptions regarding the classification of tested animals by age and cause of death, called surveillance streams. These surveillance streams are described as: healthy

slaughter, fallen stock, casualty slaughter, or clinical suspect (Wilesmith *et al*. 2004, 2005). In consultation with U.S. animal health surveillance analysts, Canadian Food Inspection Agency (CFIA) officials organized the available Canadian BSE surveillance evidence as input data for the BSurvE model (Murray 2006).

2.2 Canadian Cattle Population Size and Age Structure

BSurvE relies on the female cattle population data because (1) the information is more demographically stable and more readily available than for males, and (2) females comprise the majority of the standing adult cattle population (Wilesmith *et al*. 2005). Murray (2006) derived the number of Canadian animals in the beef and dairy reproductive female populations from cattle inventory data reported by Statistics Canada (2004). Because age-specific mortality rates and slaughter rates are unavailable for the Canadian cattle population, the population estimates were stratified by age based on the cattle population demographics estimated for the U.S. by the "Harvard-Tuskegee Study" (Cohen *et al*. 2003). It is reasonable to assume that the same rates would be applicable to Canada as the cattle industries in both countries are virtually identical. For example, the relative proportion of beef and dairy cattle (80% and 20% respectively), management practices (such as breeding, feeding and rearing), and slaughtering practices are essentially the same in both countries (NASS 2006, Statistics Canada 2001). The age-specific population profiles for the beef and dairy population were combined to give an overall estimate of the age-specific profile of the Canadian cattle population. These data (Table 1) are entered in BSurvE as the "idealized count" for age distribution. This distribution results in an estimated adult (2+ years of age) Canadian cow population of 5,979,757 animals.

Murray (2006) provides the age distribution for animals up to 20 years of age. However, for the purpose of characterizing the age distribution, BSurvE only accepts count data for cattle up to 16 years of age. BSurvE uses the cattle age distribution to calculate exit constants. These constants represent age-specific rates of removal from the herd. The decision to exclude cattle 17 to 20 years of age results in no change in the estimated exit rates, while the alternative of redistributing animals estimated to be over 16 years of age into younger age groups would have artificially altered the exit rate assumptions used in deriving the distribution and affected the BSE surveillance point calculations.

Table 1. Age Distribution for Canadian Cattle Population

Age (years)	Female Cattle
0	1,194,932
1	1,104,087
2	1,065,899
3	965,795
4	856,719
5	723,068
6	561,567
7	434,748
8	331,917
9	257,258
10	201,542
11	159,075
12	126,201
13	100,468
14	80,169
15	64,071
16	51,260

2.3 BSE Testing and Surveillance Data

2.3.1 December 2003 Washington State Case and Investigation Test Data

Because the animal was born in Canada, the BSE case detected in Washington State and confirmed in December 2003 was included as a Canadian case for the purpose of estimating the prevalence of BSE in Canada. None of the results of tests of Canadian cattle in the U.S. conducted during the epidemiologic investigation of the December 2003 case were included. That is, the BSE positive animal was included in the numerator, but none of the corresponding negative results were considered in the denominator of this analysis. Similarly, the analysis excludes the negative results of all of the BSE tests conducted in the course of epidemiologic investigations of the other eight BSE cases of Canadian origin confirmed to date in North America. Thus, only those samples collected as part of Canada's BSE surveillance program were included in the denominator of the analysis. Excluding the negative results from animals tested in follow-up investigations acts to overstate prevalence, but these negative results increase confidence that no unidentified cases are present in local association with the BSE positive animals.

2.3.2 BSE Surveillance Streams

BSurvE requires that the BSE test data be stratified by surveillance stream and age of animal. In accordance with World Organization for Animal Health (OIE) guidelines for BSE surveillance (OIE 2006), Canada's enhanced BSE surveillance program specifically targets certain risk groups amongst which BSE cases are much more likely to be found (CFIA 2006):

- cattle of all ages displaying clinical signs consistent with BSE (clinical suspects)

- cattle over 30 months of age from the 4-D categories:
    - animals found dead (dead stock)
    - animals that are non-ambulatory (downers)
    - animals presented for emergency slaughter (dying)
    - animals sent to slaughter that are found to deviate from normal behavior or appearance at ante mortem inspection (diseased)

BSurvE (Wilesmith *et al*. 2004, 2005) uses four surveillance streams which are related to the risk groups targeted in Canada as follows:

- healthy slaughter (not included in Canada's surveillance program)
- fallen stock (equivalent to Canada's dead stock category)
- casualty slaughter (equivalent to Canada's categories for downers, dying and diseased animals)
- clinical suspects

Animals are not specifically identified as BSE clinical suspects in the CFIA's laboratory database. However, Murray (2006) estimated the likely number of clinical suspects by determining which BSE related laboratory accessions could reasonably be classified as clinical suspects on the basis of the following selection criteria:

OIE (2006, Article 3.8.4.2) defines cattle displaying behavioral or clinical signs consistent with BSE as those that are affected by illnesses that are refractory to treatment AND display progressive behavioral changes (excitability, persistent kicking when milked, changes in herd hierarchical status, hesitation at doors, gates and barriers) OR display progressive neurological signs without signs of infectious illness.

To satisfy these conditions and classify an animal as a clinical suspect, Murray (2006) determined that the pathology history would need to indicate that an animal was suffering from a chronic condition (at least one week), loss of productivity, weight loss AND some sort of neurological symptom such as ataxia or behavioral changes such as nervousness or apprehensiveness. Animals suspected of rabies also were classified as clinical suspects. In classifying clinical suspects, Murray (2006) ruled out: short term conditions (duration of less than one week); injuries associated with recent calving (obturator paralysis etc.); signs of infectious illness such as Johne's disease; other explanations for locomotory disturbance such as sole ulceration; conditions that had been present for longer than six months; and unilateral lameness.

2.3.3 Tests from Animals of Unknown Age

Where birth records are unavailable, the age of animals may be estimated by dentition. Historically, the age of animals tested under Canada's BSE surveillance program has not been routinely captured. However, age associated data is available for approximately 50% of the BSE tests undertaken within CFIA's TSE network laboratories in 2004 and 2005. This subset represents over 20,000 animals. Considering the large number of animals with age data and the lack of appreciable differences in age related trends among

these years, a pooled estimate of age stratification for each BSurvE surveillance stream was determined. Murray (2006) used this estimate to stratify the surveillance results for tested animals where age was unavailable.

2.3.4 Stratified Canadian BSE Surveillance Data

Murray (2006) provides the available Canadian BSE surveillance data collected from 1992 through August 15, 2006, stratified by age and surveillance stream. However, under OIE (2006), BSE surveillance points only remain valid for 7 years. Therefore, the estimated prevalence of BSE in Canada is based on surveillance data accumulated over a 7-year period beginning August 16, 1999 and ending August 15, 2006. This surveillance period includes the 9th BSE case of Canadian origin confirmed on August 23, 2006. Since the surveillance data are reported on a calendar year basis, the number of samples for the 1999 strata was reduced proportionately to the extra months of data captured for 2006 (i.e., the 1999 data were reduced by 62.5%, or prorated to 4.5 months). Table 2 presents the surveillance testing data stratified in the BSurvE format used to estimate the prevalence of BSE in Canada.

Table 2. Canadian BSE surveillance stream test data for 16 Aug. 1999 – 15 Aug. 2006

Testing Year	Age	Fallen stock tested	Fallen stock positive	Casualty slaughter tested	Casualty slaughter positive	Clinical suspects tested	Clinical suspects positive
2006 thru Aug 15	<2yo	0	0	6	0	10	0
	2	333	0	233	0	0	0
	3	1724	0	1020	0	12	0
	4	2072	0	1443	1	17	0
	5	2210	0	1546	0	35	0
	6	2425	1	1490	0	25	1
	7	1655	0	1079	0	8	0
	8	2247	0	1427	0	14	0
	9	981	0	700	0	4	0
	10	2255	0	1575	0	27	1
	11	560	0	480	0	6	0
	12	1716	0	1447	0	14	0
	13	568	0	423	0	10	0
	14	799	0	755	0	10	0
	15	811	0	818	0	6	1
	16	414	0	368	0	0	0
	17+	353	0	490	0	8	0

Table 2 (cont'd)

Testing Year	Age	Fallen stock tested	Fallen stock positive	Casualty slaughter tested	Casualty slaughter positive	Clinical suspects tested	Clinical suspects positive
2005	<2yo	0	0	5	0	2	0
	2	486	0	484	0	17	0
	3	3007	0	1644	0	26	0
	4	3493	0	2019	0	31	0
	5	3896	0	2271	0	53	0
	6	4387	0	2330	0	36	0
	7	2795	0	1602	0	26	1
	8	3404	0	2175	0	42	0
	9	1699	0	1125	0	20	0
	10	3778	0	2692	0	54	0
	11	950	0	798	0	17	0
	12	2504	0	2160	0	25	0
	13	755	0	703	0	14	0
	14	1101	0	923	0	16	0
	15	1163	0	1232	0	25	0
	16	302	0	352	0	9	0
	17+	559	0	549	0	14	0
2004	<2yo	0	0	2	0	1	0
	2	185	0	217	0	7	0
	3	1143	0	737	0	11	0
	4	1328	0	905	0	13	0
	5	1480	0	1018	0	23	0
	6	1667	0	1044	0	15	0
	7	1062	0	718	0	11	0
	8	1294	0	975	0	18	1
	9	646	0	504	0	9	0
	10	1436	0	1207	0	24	0
	11	361	0	358	0	7	0
	12	952	0	968	0	11	0
	13	287	0	315	0	6	0
	14	418	0	414	0	7	0
	15	442	0	552	0	11	0
	16	115	0	158	0	4	0
	17+	212	0	246	0	6	0

Table 2 (cont'd)

Testing Year	Age	Fallen stock tested	Fallen stock positive	Casualty slaughter tested	Casualty slaughter positive	Clinical suspects tested	Clinical suspects positive
2003	<2yo	0	0	0	0	1	0
	2	19	0	39	0	11	0
	3	117	0	131	0	18	0
	4	136	0	161	0	21	0
	5	152	0	181	0	35	0
	6	171	0	185	2	24	0
	7	109	0	128	0	18	0
	8	133	0	173	0	28	0
	9	66	0	90	0	14	0
	10	147	0	214	0	36	0
	11	37	0	64	0	11	0
	12	98	0	172	0	17	0
	13	29	0	56	0	9	0
	14	43	0	73	0	10	0
	15	45	0	98	0	17	0
	16	12	0	28	0	6	0
	17+	22	0	44	0	9	0
2002	<2yo	0	0	1	0	2	0
	2	6	0	52	0	18	0
	3	38	0	178	0	28	0
	4	45	0	219	0	33	0
	5	50	0	246	0	56	0
	6	56	0	253	0	38	0
	7	36	0	174	0	28	0
	8	43	0	236	0	44	0
	9	22	0	122	0	21	0
	10	48	0	292	0	57	0
	11	12	0	86	0	18	0
	12	32	0	234	0	26	0
	13	10	0	76	0	15	0
	14	14	0	100	0	16	0
	15	15	0	134	0	26	0
	16	4	0	38	0	10	0
	17+	7	0	60	0	15	0

Table 2 (cont'd)

Testing Year	Age	Fallen stock tested	Fallen stock positive	Casualty slaughter tested	Casualty slaughter positive	Clinical suspects tested	Clinical suspects positive
2001	<2yo	0	0	0	0	2	0
	2	0	0	20	0	25	0
	3	0	0	68	0	39	0
	4	0	0	84	0	45	0
	5	0	0	94	0	77	0
	6	0	0	97	0	52	0
	7	0	0	67	0	39	0
	8	0	0	90	0	61	0
	9	0	0	47	0	29	0
	10	0	0	112	0	79	0
	11	0	0	33	0	25	0
	12	0	0	90	0	36	0
	13	0	0	29	0	20	0
	14	0	0	38	0	23	0
	15	0	0	51	0	36	0
	16	0	0	15	0	14	0
	17+	0	0	23	0	20	0
2000	<2yo	0	0	0	0	2	0
	2	0	0	12	0	18	0
	3	0	0	40	0	28	0
	4	0	0	50	0	33	0
	5	0	0	56	0	56	0
	6	0	0	57	0	38	0
	7	0	0	39	0	28	0
	8	0	0	54	0	44	0
	9	0	0	28	0	21	0
	10	0	0	66	0	58	0
	11	0	0	20	0	18	0
	12	0	0	53	0	26	0
	13	0	0	17	0	15	0
	14	0	0	23	0	16	0
	15	0	0	30	0	26	0
	16	0	0	9	0	10	0
	17+	0	0	14	0	15	0

Table 2 (cont'd)

Testing Year	Age	Fallen stock tested	Fallen stock positive	Casualty slaughter tested	Casualty slaughter positive	Clinical suspects tested	Clinical suspects positive
1999* (37.5% of total in strata)	<2yo	0	0	0	0	1.125	0
	2	0	0	1.5	0	10.5	0
	3	0	0	5.25	0	16.125	0
	4	0	0	6.75	0	18.75	0
	5	0	0	7.5	0	32.25	0
	6	0	0	7.875	0	21.75	0
	7	0	0	5.25	0	16.125	0
	8	0	0	7.125	0	25.5	0
	9	0	0	3.75	0	12.375	0
	10	0	0	9	0	33	0
	11	0	0	2.625	0	10.5	0
	12	0	0	7.125	0	15	0
	13	0	0	2.25	0	8.625	0
	14	0	0	3	0	9.375	0
	15	0	0	4.125	0	15	0
	16	0	0	1.125	0	5.625	0
	17+	0	0	1.875	0	8.625	0

*Data prorated for 1999. See accompanying text.

2.4 Feed Ban Evidence

Canada introduced a feed ban in 1997. The Canadian BSE surveillance program has been intensified since the first native case was detected in 2003, and the surveillance data available to date indicate that the country's feed ban has kept the level of disease in subsequent birth year cohorts at a low level. Due to BSE's long incubation period and the low prevalence of BSE in Canada, however, the available surveillance data provides limited information about the trajectory of disease incidence over time. However, implementation of feed mitigations has been demonstrated to dramatically decrease the risk of new BSE cases, and this knowledge provides information about the status of disease before consideration of the animal health surveillance data. For the purpose of this analysis, empirical evidence following the 1988 UK feed ban provides prior information about the effect of a reasonably effective feed ban on the incidence of BSE. These data are used as surrogate data to predict the decline in prevalence in Canadian cattle cohorts born after the 1997 Canadian ban.

Retrospective analysis of the incidence of BSE by birth year cohort demonstrated that the UK's BSE epidemic was on the upswing before a ruminant-to-ruminant feed ban was introduced in July 1988, but the incidence of disease declined rapidly for each cohort of cattle born after the ban (Schreuder *et al*. 1997). As clearly shown in the epidemic curve (Figure 1), the UK ruminant-to-ruminant feed ban introduced in 1988 substantially decreased the number of new cases in subsequent birth year cohorts, although it was insufficient to eradicate the disease immediately.

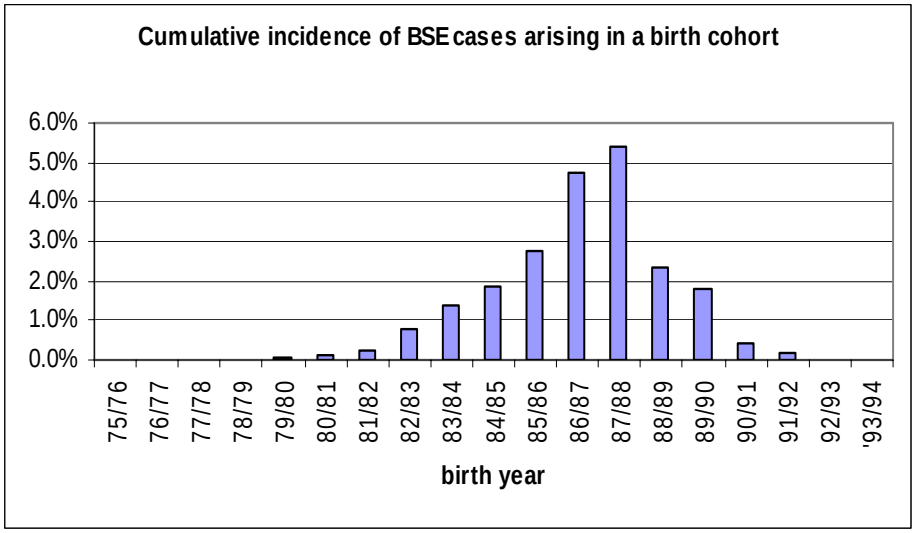

Figure 1. Cumulative incidence of BSE in the UK by birth year cohort.
Source: Schreuder *et al*. (1997)

Applying the method described by Schreuder *et al*. (1997) to the cumulative UK BSE surveillance data available as of November 2005 (DEFRA 2005), Animal and Plant Health Inspection Service (APHIS) Centers for Epidemiology and Animal Health (CEAH) staff updated the cumulative incidence for each UK birth year cohort (Table 3). In comparison to the initial ruminant-to-ruminant feed ban introduced in the UK in 1988, the Canadian feed ban introduced in 1997 is considered equivalent or more restrictive, prohibiting feeding of most mammalian proteins to ruminants. In 1994, the UK feed ban was amended to become a more restrictive mammalian-to-ruminant feed ban. Therefore, the UK-based evidence about the effect of a feed ban on BSE prevalence was incorporated into the analysis for Canadian cohorts born in the first five years following Canada's 1997 rule. Thus, the Canadian feed ban was assumed to be at least as effective as the first five years of the initial UK feed ban (Table 3).

Table 3. Observed (UK) and Expected (Canada) Decline in BSE Incidence by Birth Year Cohort Following Feed Ban Introduction

Years since feed ban	UK Birth cohort	BSE cases in the UK cohort	Proportion of the 1987/88 UK cohort's incidence	Canadian Birth cohort	Years since feed ban	Expected proportion of the 1997 Canadian cohort's incidence *
0	1987/88	39201	1.0000	1997	0	1.0000
1	1988/89	16556	0.4223	1998	1	0.4223
2	1989/90	11044	0.2817	1999	2	0.2817
3	1990/91	5036	0.1285	2000	3	0.1285
4	1991/92	4348	0.1109	2001	4	0.1109
5	1992/93	3231	0.0824	2002	5	0.0824
6	1993/94	2517	0.0642	2003	6	n/a
7	1994/95	1675	0.0427	2004	7	n/a
8	1995/96	444	0.0113	2005	8	n/a

*Assuming Canadian feed ban was as effective as the initial UK feed ban in its first five years.

Additional information provided by Cohen *et al*. (2003) indicates that the prevalence of BSE is expected to decline in the U.S. in response to the domestic feed ban. U.S. epidemiologists reviewed records and conducted site visits to Canadian facilities to evaluate the Canadian feed ban, its implementation and compliance. USDA (2005) concluded that the Canadian feed ban is not substantially different from the U.S. feed ban. Because the Canadian ban is similar to the U.S. ban and deemed to be effectively enforced, the decline predicted by Cohen *et al*. (2003) would likely apply to the Canadian population as well. In sum, knowledge of the effect of a feed ban provides substantial information about BSE prevalence before consideration of the surveillance data.

3. Methods

3.1 BSurvE Model

The BSurvE model was developed to provide a method for evaluation of national surveillance data and optimization of national surveillance strategies for BSE (Wilesmith *et al*. 2004). BSurvE uses epidemiologic information about the disease that was accumulated during the UK and European outbreaks to predict parameters such as incubation period of BSE, probable length of an infected animal's life, and the dynamics of disease expression in infected animals. BSurvE combines this information with country-specific demographic information about a national herd (size and age distribution) and national BSE surveillance data to achieve a set of point values for samples taken from cattle of different age and surveillance streams—healthy slaughter, fallen stock, casualty slaughter, or clinical suspect. The points represented by an animal tested for BSE are based on the relative likelihood that the disease would be detected in an animal leaving the herd at a particular age and by a particular surveillance stream. Under this scheme, one point is equivalent to an animal randomly selected for testing from the national herd (Wilesmith *et al*. 2004).

The BSurvE model is implemented as a Microsoft© Excel™ spreadsheet application. The analysis herein based on the BSurvE model was performed using BSurvE Version 06.03 (downloaded March 22, 2006 from http://www.bsurve.com). The BSurvE spreadsheet model and documentation are available on the BSurvE website (http://www.bsurve.com/forum/forum.asp?$sid=&id=10). The BSurvE website includes updates made to the BSurvE model when a new version is released and documentation that provides detailed description of the underlying functions of the model as well as step by step user instructions.

For the purpose of estimating the prevalence of BSE in Canada, BSurvE was used in two ways. First, for the purposes of estimating the prevalence of BSE in Canada using the Bayesian Birth Cohort (BBC) model including the UK feed ban evidence, BSE surveillance point values allocated to the 1991-2005 birth year cohorts were calculated by entering individual surveillance year data (Table 2) into the BSurvE model and then summing the BSE surveillance points calculated by the model for each birth cohort over the 7-year surveillance period ending August 15, 2006. Note that Murray (2006, Table 26) presents BSE surveillance points allocated to each birth cohort accumulated over more than 14 years, dating back to the 1992 surveillance year.

Second, for the purposes of comparison, the prevalence of BSE in Canada also is estimated using the unembellished BSurvE model application intended for application to countries where BSE is non-endemic, or where the infection rate is independent of birth year cohort, with animals from different birth year cohorts having the same underlying probability of infection. The BSurvE model developers refer to this prevalence estimation method as BSurvE Prevalence B (Wilesmith *et al*. 2004, 2005). The latter BSE prevalence estimation method makes no assumptions about feed ban efficacy and relies on the surveillance data alone. In contrast to OIE (2006), which permits accumulation of BSE surveillance points over 7 years, BSurvE (Version 06.03, downloaded 3/22/06 from http://www.bsurve.com) allows entry of no more than 5 years of surveillance data at a time. Therefore, for the purposes of estimating the prevalence of BSE in Canada using BSurvE Prevalence B, testing data (Table 2) were combined for 1999-2002 for entry into the model. Recall that the surveillance points calculated by BSurvE depend on the age and health strata of animals when they are tested and that BSurvE Prevalence B assumes a constant probability of infection over time. In contrast to BSurvE Prevalence B, the BSurvE application intended for application to countries where BSE is endemic (BSurvE Prevalence A) is designed to permit an assessment of changes in BSE prevalence across birth year cohorts. As discussed below, however, the Canadian BSE surveillance data provide no statistical basis for distinguishing BSE prevalence among birth year cohorts. Therefore, BSurvE Prevalence B is used here to provide a sensitivity analysis of the effect of incorporating the UK feed ban data on the estimated BSE prevalence in Canada, and more importantly, the overall results of the risk assessment.

3.2 Bayesian Birth Cohort Model

The Bayesian Birth Cohort (BBC) model combines prior evidence about the effect of a ruminant-to-ruminant feed ban on BSE dynamics with the surveillance points calculated by the BSurvE model, resulting in a more precise estimate of BSE prevalence. Like the BSurvE model, the BBC model prevalence estimate refers to all BSE-infected animals, regardless of whether they would be detectable or showing clinical signs. As a starting point, this method assumes that prevalence may be anything from 0 to 100% (i.e., the prior assumption was that prevalence is uniformly distributed between 0 and 100%). The model then updates the Canadian prevalence estimate based on the detected BSE cases, the expected decline in BSE incidence by birth year cohort following the first five years of the Canadian feed ban (Table 3), and the BSurvE point total for each birth year cohort assumed to contribute adult animals to the current standing population (birth years 1991-2005). The analysis considers animals tested over the 7 year surveillance period ending August 15, 2006; however, the surveillance points associated with animals born prior to 1991 do not enter the analysis under the BBC model because BSurvE only accepts data for cattle up to 16 years of age. To date, no BSE cases of Canadian origin have been detected in animals born prior to 1991.

The BBC model assumes that prevalence is constant for birth year cohorts 1991-97, with 1998 being the first cohort influenced by the 1997 feed ban. The prevalence of BSE in the adult cattle alive in 2006 was estimated as the weighted sum of the individual birth cohorts' prevalence levels, where the weights are the proportion of infected animals in each birth cohort that remain alive in 2006. The BBC model was implemented using two Bayesian analytical methods: Gibbs sampling and Sampling-Importance-Resampling (SIR).

3.2.1 Gibbs Sampling

Gibbs Sampling is a Monte Carlo Markov Chain (MCMC) statistical method (Vose 2000). MCMC methods are based on an iterative updating scheme that is repeated until the sequence of parameter vectors converges. In general, Bayesian Monte Carlo procedures update uncertainty with forward and backward propagation of the model (Brand and Small 1995). Vose (2006) recommended this method for implementing the BBC model and provided exemplar computer code using WinBUGS (Bayesian Inference Using Gibbs Sampling), a freeware statistical application. WinBUGS (Version 1.4.1, downloaded January 2006 from http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) was used to implement the BBC model using the code presented in Appendix 1. Two chains were initiated in WinBUGS to monitor convergence with starting values for prevalence (p) equal to 0.1 and 0.0001. A total of 100,000 iterations were performed, and data from the last 20,000 iterations were used for prevalence estimation.

3.2.2 Sampling-Importance-Resampling (SIR)

Using the same model inputs described above, an alternative Bayesian method was used to verify the BBC model results obtained using WinBUGS. In contrast to the iterative Gibbs sampling method, Sampling-Importance-Resampling (SIR) is a noniterative

algorithm used to simulate Bayesian posterior distributions (Rubin 1988). This procedure is also referred to as a weighted bootstrap (Smith and Gelfand 1992). In SIR, *m* samples are drawn from an initial approximation to the desired distribution, and then $l < m$ samples are randomly drawn from the first finite sample (*m*) with probability proportional to their importance (i.e., sampling weight). The rationale of the SIR algorithm is based on the fact that as $m/l \rightarrow \infty$, the *l* sample values represent independent draws from the desired posterior distribution (Rubin 1988).

In essence, the iterative MCMC procedures like Gibbs sampling converge on the desired posterior as the number of iterations approaches infinity, whereas the non-iterative SIR procedure converges to the desired posterior as the initial sample (*m*) gets infinitely larger than the resample (*l*). The SIR algorithm provides a useful check on the Gibbs procedure because the former is not prone to "getting stuck in a rut" (i.e., converging to local rather than global maxima). A disadvantage of the SIR algorithm is that its computational efficiency depends on having a good first approximation (prior), whereas the iterative procedures can be monitored for convergence and stopped once the convergence criteria are met.

The SIR algorithm proceeds by using Monte Carlo simulation methods to generate a first approximation to the pre-feed ban prevalence (*p*) uncertainty distribution that captures the entire range of feasible parameter values, evaluating the likelihood of discrete *p* values given the surveillance evidence, and then resampling from the uncertainty distribution proportional to importance weights (normalized likelihoods) of the discrete *p* values. The likelihood of *p*, given the surveillance evidence, is calculated assuming a binomial likelihood function:

$$\mathrm{Lik}(\mathrm{p} \mid \mathrm{s}) = \prod_{1991}^{2005} \mathrm{Binomial}(\mathrm{s}, \mathrm{n}, \mathrm{p})$$

where: s_i = number of BSE cases detected in the i^{th} birth year cohort
n_i = number of BSurvE points for the i^{th} birth year cohort
$p_{1991} = p_{1992} = \ldots = p_{1997} = p$
$p_{1998} = 0.4223 * p$
$p_{1999} = 0.2817 * p$
$p_{2000} = 0.1285 * p$
$p_{2001} = 0.1109 * p$
$p_{2002} = 0.0824 * p$
$p_{2003} = 0.0824 * p$
$p_{2004} = 0.0824 * p$
$p_{2005} = 0.0824 * p$

The resampling weights (w) are equal to normalized likelihood values for discrete uncertainty realizations of *p*:

$$w_m = \frac{Lik(p_m)}{\sum Lik(p)}$$

Monte Carlo methods are used to resample from the uncertainty distribution for *p*, which is assumed to follow a beta distribution, the conjugate prior to the binomial (Vose 2000):

$$p \sim Beta(\alpha, \beta)$$

Based on the mean and variance obtained from the Monte Carlo simulation of *p*, the parameters of the beta distribution are estimated by the method of matching moments (Evans *et al*. 1993):

$$\hat{\alpha} = \bar{x}\{[\bar{x}(1-\bar{x})/s^2]-1\}$$
$$\hat{\beta} = (1-\bar{x})\{[\bar{x}(1-\bar{x})/s^2]-1\}$$

Based on the posterior for *p* obtained from these parameter estimates, the prevalence in the current adult standing cattle population in Canada is estimated as the weighted sum of the individual birth cohorts' prevalence levels, where the weights are the proportion of infected animals in each birth cohort that remain alive in 2006. The SIR method was implemented using Palisades© @Risk™ (Ver. 4.5), an add-on to Microsoft© Excel™ (Ver. 9.0). Monte Carlo simulation was performed with Latin Hypercube sampling (10,000 iterations).

4. Results

4.1 BSurvE Points by Birth Year Cohort

Table 4 presents the BSE surveillance points calculated by BSurvE from the Canadian BSE surveillance data and the Canadian BSE cases by birth year cohort. The increase in surveillance points between the 2004 to 2005 birth year cohorts is due to the larger number of animals tested in the clinical and casualty surveillance streams for the 2005 cohort. This can be seen by comparing the one-year age class in Murray (2006, Tables 23 and 24).

Table 4. BSurvE Points and BSE Cases by Birth Year Cohort

Birth year	BSurvE Points	BSE Cases
1991	24,737	1
1992	35,814	0
1993	61,914	0
1994	115,950	0
1995	183,528	0
1996	225,473	2
1997	217,155	2
1998	173,111	1

1999	142,290	0
2000	150,111	2
2001	128,565	0
2002	59,090	1
2003	13,894	0
2004	558	0
2005	2,170	0

4.2 No Statistically Significant Differences between Birth Year Cohorts

To determine whether there is any empirical basis for distinguishing BSE prevalence among Canadian birth year cohorts, we consider the BSurvE points calculated for the Canadian 1991-2005 birth year cohorts. Recalling that one BSurvE point is equivalent to one randomly sampled animal, multiple comparison tests were performed using BSE surveillance points accumulated for birth year cohorts as inputs to statistical methods designed to detect differences among random samples. The results indicate that the available surveillance data provide no empirical basis for distinguishing BSE prevalence among Canadian birth year cohorts. (To maintain an overall type I (false positive) error rate when conducting multiple comparisons tests, the comparison-wise error rate must be adjusted. To maintain an overall type I error rate of 5 percent, with 105 pairwise comparisons, the comparison-wise type I error rate (CER) is set to 0.05 percent (Sidak 1967). The multiple comparison test was repeated, removing the 1991 through 2002 cohorts in sequence and modifying the CER accordingly to maintain the overall type I error rate of 5 percent. In each application of the test, there were no statistically significant differences in BSE prevalence among birth year cohorts. Similarly, no statistically significant differences were found in a simple pairwise comparison of birth cohorts born before (1991-1997) or after (1998-2005) feed ban introduction. In summary, analysis of the Canadian BSE surveillance data provides no statistical basis for distinguishing BSE prevalence among birth year cohorts. Therefore, a single prevalence was estimated for the standing adult cattle population.

In addition to the lack of statistical evidence to distinguish among cohort prevalence estimates, there are biological reasons why birth cohorts should not be considered independent. Animals born within one or two years of a positive case have a similar likelihood of being exposed to the feed sources responsible for infecting the case (given no information about feed mitigations). Knowledge of BSE incidence in animals born in each of the 3 to 7 years prior to the birth date of a BSE case would also influence the prediction of the current prevalence, because infected tissues from these animals could have been recycled into the feed of the case's birth cohort (again assuming no knowledge of feed mitigations).

4.3 Prevalence Estimates

The WinBUGS implementation of the BBC model resulted in an expected prevalence value of 0.68 per million. In comparison, the SIR implementation of the BBC model resulted in an expected prevalence value of 0.65 per million. The 95% confidence levels also were virtually the same, 1.1 and 1.0 per million, respectively. Due to the negligible

difference in the two results, the expected value of the Bayesian Birth Cohort model was taken as 0.68 per million.

Table 5 summarizes the results of the estimation of BSE prevalence in the standing Canadian adult cattle population as of August 15, 2006. Based on the expected prevalence value under the BBC model and the estimated adult herd size (Table 1), the expected number of BSE-infected animals in the standing Canadian adult cattle population is 4.1. By comparison, the expected value obtained under BSurvE Prevalence B is 3.9 per million, which corresponds to an estimated 23.2 BSE-infected animals in the standing Canadian adult cattle population.

Table 5. Estimated Prevalence of BSE in Canada

Prevalence in adult cattle population	**Bayesian birth cohort method (BBC) with UK feed ban data**	**BSurvE Prevalence B estimate without including feed ban data**
Expected value	$0.68 * 10^{-6}$	$3.9 * 10^{-6}$
95% confidence level	$1.1 * 10^{-6}$	$6.8 * 10^{-6}$

It is important to note that the estimated prevalence distribution presented here represents uncertainty and not variability. At a given point in time, the proportion (i.e., probability) of infected animals in the population is a fixed value, but the exact magnitude of the value is uncertain. Further, assuming the probability of infection remains constant, the actual number of infected cattle in the population would still vary randomly about the mean of the probability distribution over time. Similarly, if we repeatedly draw a sample of animals from a population with a fixed prevalence (i.e., fixed probability of infection), the proportion of infected animals would vary randomly between samples. Assuming a constant probability of infection, the random variability in the number of BSE infected animals in the adult cattle population would follow a binomial distribution that is described by the prevalence and size of the population (Vose 2000). For a large sample size and low prevalence values, the Poisson distribution approximates the binomial variability distribution and is incorporated in the model supporting the exposure assessment for live bovines ([Section IV.A. and Attachment 2]) to represent variability around the prevalence estimates generated here.

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Appendix 1. WinBUGS Code Used to Implement BBC Model

Calculate probabilities of infection in each year. Probability of infection is assumed constant until the implementation of the feed ban in 1997. The level of reduction in each of the 5 years after the implementation of the ban is based on BSE incidence data from DEFRA (2005) based on methods described in Schreuder et al. (1997). The reductions only apply to first 5 years following the ban. After 5 years, there is assumed no further reduction associated with the ban.

```
model{
# Set prior
        P ~ dbeta(1,1) #prevalence in Population in year of Canadian ban

        P1991 <- P
        P1992 <- P
        P1993 <- P
        P1994 <- P
        P1995 <- P
        P1996 <- P
        P1997 <- P
        P1998 <- P*0.4223
        P1999 <- P*0.2817
        P2000 <- P*0.1285
        P2001 <- P*0.1109
        P2002 <- P*0.0824
        P2003 <- P*0.0824     # Set as conservatively high
        P2004 <- P*0.0824
        P2005 <- P*0.0824

# Calculate expected infections for the number of points accumulated for each year

                L1991 <- P1991*24737
                L1992 <- P1992*35814
                L1993 <- P1993*61914
                L1994 <- P1994*115950
                L1995 <- P1995*183528
                L1996 <- P1996*225473
                L1997 <- P1997*217155
                L1998 <- P1998*173111
                L1999 <- P1999*142290
                L2000 <- P2000*150111
                L2001 <- P2001*128565
                L2002 <- P2002*59090
                L2003 <- P2003*13894
                L2004 <- P2004*558
                L2005 <- P2005*2170
```

Match Poisson(expected infections for points accumulated in year) to observed infections

S1991 ~ dpois(L1991)
S1992 ~ dpois(L1992)
S1993 ~ dpois(L1993)
S1994 ~ dpois(L1994)
S1995 ~ dpois(L1995)
S1996 ~ dpois(L1996)
S1997 ~ dpois(L1997)
S1998 ~ dpois(L1998)
S1999 ~ dpois(L1999)
S2000 ~ dpois(L2000)
S2001 ~ dpois(L2001)
S2002 ~ dpois(L2002)
S2003 ~ dpois(L2003)
S2004 ~ dpois(L2004)
S2005 ~ dpois(L2005)

# Sum [Prevalence in each year * number from each cohort expected to remain standing in the 2005 Canadian population]
InfectedNow <- (0.0002 * P1991 + 0.0005 * P1992 + 0.001 * P1993 + 0.0017 * P1994 + 0.0042 * P1995 + 0.0093 * P1996 + 0.0186 * P1997 + 0.0344 * P1998 + 0.0667 * P1999 + 0.131 * P2000 + 0.2538 * P2001 + 0.4659 * P2002 + 0.6811 * P2003 + 0.8002 * P2004 + 0.8902 * P2005) * 1194932
PrevNow <- InfectedNow / 5979757
}

Data
# A list of the observed BSE cases in each year
list(S1991 = 1, S1992 = 0, S1993 = 0, S1994 = 0, S1995 = 0, S1996 = 2, S1997 = 2, S1998 = 1, S1999 = 0, S2000 = 2, S2001 = 0, S2002 = 1, S2003 = 0, S2004 = 0, S2005 =0)

Initial values
# Two chains with different values for P to monitor convergence of the estimates
list(P=0.1)
list(P=0.0001)

The output (node) is PrevNow

Harvard Model of Bovine Spongiform Encephalopathy
Implications of Importing Cattle Over 30 Months of Age from Canada

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Executive Summary

The analysis described here has been conducted for USDA-APHIS, as a component of a risk assessment conducted to evaluate the impact of allowing additional cattle imports from BSE minimal-risk regions. Specifically, this analysis supports the exposure assessment component of the risk assessment and contributes to the environmental assessment.

In January 2005, USDA-APHIS published a final rule allowing some cattle imports from countries falling into a new category, designated "minimal risk regions". The rule places Canada into the minimal risk regions category and allows that country to export cattle to the U.S., so long as the animals are slaughtered prior to the age of 30 months. In order to investigate the impact of allowing the import of older cattle from Canada into the U.S. and eliminating the requirement that they be slaughtered by a specified age, APHIS conducted a risk assessment. The risk assessment estimates the likelihood that BSE-infected cattle will be imported into the U.S. given the mitigations proposed (the release assessment), the extent to which disease might spread among U.S. cattle as a result (the exposure assessment), and characterizes the resulting impacts (consequence assessment). This document supports the environmental assessment and the exposure assessment component of the risk assessment.

The analysis uses a computer simulation model developed for USDA by the Harvard Center for Risk Analysis[1]. A series of modifications to the model have been implemented. The most important modifications for the purpose of this analysis include enhanced capabilities for specifying the import of infected cattle; and explicit modeling of cattle exposure to the BSE agent via administration of poultry litter in cattle feed. For the purpose of completeness, this report documents all modifications to the function of the model and to its assumptions made since the release of initial Harvard BSE risk assessment (1).

In order to characterize the impact of uncertainty, the analysis evaluates the impact of using pessimistic assumptions for the rate of mislabeling and contamination, the rate of on-farm misfeeding of prohibited feed to cattle, the prevalence of various rendering technologies used in

[1] While on the research staff at the Harvard Center for Risk Analysis, the author of this report was a lead developer of the Harvard BSE simulation model. He has been involved in several risk assessments conducted using that software. Dr. Cohen moved to the Tufts New England Medical Center in January, 2006.

the U.S., the proportion of poultry litter that is used in cattle feed, and the prevalence of BSE in Canada.

Under base case conditions, the results of this analysis indicate that the expected number of infected cattle in the U.S. over 20 years as a result of importing cattle from Canada would amount to 21 animals. Most of these infected animals (approximately 90%) would be imported directly, while the remaining 10% would represent secondary infections (*i.e.*, native U.S. cases). Potential human exposure over this 20-year period would be expected to amount to 45 cattle oral ID_{50}s. Of the five uncertain parameters considered in the sensitivity analyses, the model is most sensitive to the release of infectivity (as expressed by BSE prevalence in Canada). Simultaneous assignment of pessimistic values to all five of the uncertain assumptions considered here increases the predicted number of secondary BSE cases to 42 on average, with total potential human exposure increasing to 290 cattle oral ID_{50}s over 20 years. Under all cases, the reproductive constant for BSE (R_0) remains less than 1 with high probability, indicating exponential growth in the number of native U.S. cases following potential release from Canada is unlikely. Equivalently, the results indicate that in the absence of a continual release of BSE into the U.S., its prevalence will decrease over time, eventually leading to its elimination. It is important to note that this set of findings reflects the simultaneous use of pessimistic values for a range of assumptions, including the assumptions identified as being influential in earlier analyses (1), as well as the assumed prevalence of BSE in Canada.

1 Introduction

The analysis described here has been conducted for the USDA Animal and Plant Health Inspection Service (APHIS) as part of a risk assessment conducted to evaluate the impact of allowing additional cattle imports from BSE minimal-risk regions. Specifically, this analysis supports the exposure assessment component of the risk assessment and contributes to the environmental assessment.

In response to Canada's May 2003 discovery of a dairy cow in Alberta province infected with bovine spongiform encephalopathy (BSE), the U.S. Department of Agriculture (USDA) banned the import of cattle from that country. The border closure reflected U.S. policy that prohibited such imports from countries with indigenous cases of BSE. Since that initial discovery, eight additional BSE-infected cattle from Canada have been discovered, one of which had been exported to the U.S.

In January 2005, USDA-APHIS published a final rule allowing some cattle imports from countries falling into a new category, designated "minimal risk regions". The rule places Canada into the minimal risk regions category and allows that country to export cattle to the U.S., so long as the animals are slaughtered prior to the age of 30 months. In order to investigate the impact of allowing the import of older cattle from Canada into the U.S. and eliminating the requirement that they be slaughtered by a specified age, APHIS conducted a risk assessment. The risk assessment estimates the likelihood that BSE-infected cattle will be imported into the U.S. given the mitigations proposed (the release assessment), the extent to which disease might spread among U.S. cattle as a result (the exposure assessment), and characterizes the resulting impacts (consequence assessment). This document supports the environmental assessment and the exposure assessment component of the risk assessment.

The analysis described here uses the BSE simulation developed by the Harvard Center for Risk Analysis (HCRA) (1;2). Using this model, the analysis estimates the extent to which the release of BSE from Canada will contribute to the prevalence of BSE among cattle in the U.S. In addition to describing the contribution to prevalence, the model also describes the ability of safeguards in the U.S. to eliminate BSE in terms of the disease's reproductive constant, designated R_0. The R_0 parameter is the average number of new BSE cases resulting from each existing BSE case. A value of R_0 greater than 1.0 indicates that prevalence increases over time

(because each existing case gives rise to more than one new case on average), while a value of R_0 less than 1.0 indicates that prevalence decreases over time. The HCRA BSE model reports other information, including the potential for human exposure to the BSE agent.

Strictly speaking, an analysis of the impact of eliminating age restrictions on cattle imports from Canada would compare the proposed regulation to the status quo, which, as noted above, allows the import of cattle from Canada, so long as they are slaughtered prior to the age of 30 months. This analysis develops a more conservative "bounding" estimate of the incremental impact of eliminating age restrictions on animal health and human exposure because it does not "subtract" risks associated with status quo policies.

In addition to the base case scenario, this analysis presents sensitivity analyses to evaluate the impact of alternative plausible assumptions identified in earlier work (1;2) as having the most important impact on the simulation results. In addition to evaluating the impact of these assumptions, this assessment also investigates the impact of assigning pessimistic values to the proportion of poultry litter used in cattle feed, and to the prevalence of BSE in Canada.

The remainder of this paper has two sections. Section 2 describes the methodology, including parameter assumptions and revisions to the Harvard simulation model for this project. Section 3 details results and discusses the findings.

2 Methods

The BSE simulation model used in this analysis was first described by Cohen *et al.* (1;2). The functionality of that model has since been modified to accommodate the requirements of an analysis conducted for the USDA Food Safety Inspection Service (FSIS) to evaluate regulatory changes that influence the risk pathway. Section 2.1 describes the modifications, as well as additional modifications that have been made for this analysis. The base case scenario builds on the base case analysis described by Cohen *et al.* (1) and subsequently revised for FSIS in Cohen and Gray (3). Section 2.2 describes the base case scenario for this analysis representing conditions in the U.S. if imports of older cattle from Canada are allowed. Finally, Section 2.3 describes sensitivity analyses conducted for the purpose of characterizing the extent to which the findings of this analysis depend on assumptions made for critical parameters.

Note that the analysis conducted for FSIS represents a "layer" of simulation and parameter revisions made on top of the original BSE model described by Cohen *et al.* in October 2003 (1). The analysis described here therefore represents a second layer of simulation and parameter revisions. In order to save the reader the trouble of having to refer back to both of the previous documents and sequentially reconstructing the series of changes described, this document effectively subsumes the relevant changes to the FSIS report (3) and incorporates text from that report as needed to describe the changes that were made as part of that effort. Where appropriate, this document indicates where material has been taken verbatim or with some modifications from that report.

Finally, note that, as described in the introduction to the methodology section in the FSIS report, this analysis uses central estimates for the base case assumptions where possible. However, in the few limited cases where doing so is not feasible, this analysis attempts to err on the side of using assumptions that overstate the extent to which BSE might spread in the U.S. (*i.e.*, so-called "conservative" assumptions). To the extent that the findings here show that release of BSE into the U.S. does not pose a substantial risk, the use of these conservative assumptions does not compromise the qualitative implications of this report's findings. In any case, use of conservative values was largely limited to parameters that, based on earlier work (1), are known not to have a substantial impact on the simulation results.

2.1 Revisions to the Harvard Simulation Model

Eight sets of changes to the Harvard simulation model have been implemented for the purpose of this and other analyses conducted since the release of the assessment conducted by Cohen *et al.* (1). This section describes those changes. These include changes made for FSIS (3): addition of ambulatory status as a characteristic that factors into *antemortem* inspection findings (Section 2.1.1); changes to the operation of the *antemortem* inspection process (Section 2.1.2); addition of tonsils as a tissue category (Section 2.1.3); changes to SRM inspection (Section 2.1.4); addition of supplemental reports that detail contamination of human food by animal age and ambulatory status (not used in this report) (Section 2.1.5); and changes made specifically for APHIS in this analysis: enhanced capabilities for specifying the import of infected cattle over the course of the simulated period (Section 2.1.6); separate specification of SRM inspector, rendering, and disposition of rendered material (MBM transport) for healthy slaughter and dead animals (Section 2.1.7); and explicit modeling of cattle exposure to the BSE agent via

administration of poultry litter in cattle feed (Section 2.1.8). Sections 2.1.1 through 2.1.5 are taken directly from Cohen and Gray (3), and the remaining three sections are new.

It should be emphasized that not all of these capabilities are used in all analyses, and in particular, this analysis uses only a subset of the capabilities described here. Section 2.2 describes the specific assumptions made for this analysis.

2.1.1 Ambulatory Status (From Cohen and Gray (3))

USDA now prohibits the use of non-ambulatory animals for human food. In order to represent this policy in the simulation model, along with others that may place restrictions on the use of these animals in feed, the simulation has been modified so that it tracks the ambulatory status of cattle infected with BSE. The simulation can designate an animal as non-ambulatory when the animal becomes infected with BSE or when the animal develops clinical signs of BSE. Once an animal becomes non-ambulatory, it cannot become ambulatory at a later time during the simulation. This framework is consistent with non-ambulatory status being assigned to an animal at *antemortem* inspection. Appendix 1 details the assignment of parameter values to control this feature.

2.1.2 Operation of the *Antemortem* Inspector (From Cohen and Gray (3))

Tasks performed by the *antemortem* inspector are now divided into two steps. As part of the first step, inspection, the *antemortem* inspector determines 1) whether the animal passes inspection based on considerations not related to BSE, and 2) whether the animal shows clinical signs of BSE. As part of the second step, allowed use designation, the *antemortem* inspector designates the animal as allowed for use in human food, animal feed, or both feed and food based on the two determinations made in the inspection step, and on the animal's ambulatory status.

Inspection: The *antemortem* inspector makes two judgments. First, it determines if the animal passes or fails inspection based on considerations not related specifically to the manifestation of clinical BSE signs. The probability that an animal will pass inspection based on non-BSE considerations depends on 1) its ambulatory status, and 2) its age. The second determination made by the *antemortem* inspector is whether the animal displays clinical signs of BSE. This finding depends on the animal's ambulatory status and on whether the animal is, in

fact, clinical. Note that it is possible for the inspector to fail to identify a clinical animal as displaying BSE signs. That is, this feature makes false negative findings possible.

Allowed use designation: The *antemortem* inspector follows two sets of deterministic rules, one of which governs whether an animal can be used in human food, and the other which governs when an animal can be used in animal feed. In both cases, the designation depends on three factors: 1) whether the animal passed inspection for non-BSE related factors, 2) whether the *antemortem* inspector identified the animal as displaying clinical signs of BSE, and 3) whether the animal is non-ambulatory.

Appendix 1 details the assignment of parameter values to control the behavior of the *antemortem* inspector. As configured for the analyses described in this report, the *antemortem* inspector prohibits use of cattle tissue in feed only if the animal displays clinical signs of BSE. Although in reality, there is no such explicit requirement governing *antemortem* inspection, this characterization of the *antemortem* inspector's operation makes sense within the context of the simulation model. In particular, the simulation explicitly models only animals that have been infected with BSE. Moreover, the base case assumes that only animals that have reached the clinical stage of disease display clinical signs consistent with BSE. In the "real world," such animals would be most likely tested for the BSE agent after slaughter and would test positive with very high probability (because they have reached the end of the incubation period and because the screening tests are geared to minimize false negative results). After testing positive, the carcasses from such animals would be destroyed. That is, as is effectively assumed in the simulation, the tissue from such animals could not be used in either human food or in animal feed.

2.1.3 Tonsils (From Cohen and Gray (3))

Tonsils have been added as a tissue category.

2.1.4 SRM Inspection (From Cohen and Gray (3))

The original BSE simulation model (1) eliminated infectivity using the SRM inspector only when animals were sent to slaughter. That is, the SRM ban did not apply to dead stock. The model has been revised so that it can remove infectivity from dead stock, as well.

2.1.5 Supplemental Reports (From Cohen and Gray (3))

The simulation model can now report distributions for the number of cattle oral ID_{50}s in human food (by tissue) for cattle by age range and ambulatory status. As now configured, the simulation can create separate reports for each combination of the following age ranges (0 to 11 months, 0 to 23 months, 0 to 29 months, 30+ months, and all ages) and ambulatory status designations (normal, non-ambulatory).

2.1.6 Import of Infected Cattle

The original model allowed the import of infected cattle only once, at the beginning of the simulation. The model now allows for the periodic import of infected cattle. The model allows the specification of the animal type (dairy, beef slaughter, or reproductive beef), gender, age at import, the import rate for infected animals (i.e., the Poisson distribution parameter), the age at infection, and optionally, a scheduled slaughter age. This last parameter can be used to specify that animals must be slaughtered within a fixed amount of time after import. Alternatively, if no specific slaughter age is specified, the simulation assimilates the animals into the U.S. cattle population and slaughters them at random using the appropriate probabilities specified for native U.S. cattle.

2.1.7 Separate Slaughter and MBM Production for Dead and Healthy Slaughter Cattle

The revised simulation model now allows for the specification of distinct parameter values governing SRM inspection, rendering, and disposition of processed proteins for dead and healthy slaughter cattle. The revision was made to allow for the possibility that the segment of the rendering industry that processes dead animals is distinct from the segment of the industry that processes healthy slaughter animals. In addition, it is possible that the effectiveness of SRM removal for healthy slaughter animals will differ from the corresponding effectiveness for dead cattle.

Because the model allows distinct specification of rendering, SRM inspection and processed tissue disposition for dead and healthy slaughter cattle, a feature has been added that allows non-ambulatory cattle to be treated like either dead cattle or like healthy slaughter animals. If the user chooses to treat non-ambulatory cattle like dead cattle, tissue from these animals will not be available for human consumption. In addition, 1) the SRM inspector, renderer, and MBM

transport parameters for dead animals will govern processing of non-ambulatory animals; 2) non-ambulatory cattle will be disposed of on the farm with the same probability as animals that die on the farm; and 3) the use of such cattle in animal feed is subject to restrictions imposed by *antemortem* inspection. If the user chooses to treat non-ambulatory animals like healthy slaughter animals, then the tissue from these animals can be used in human food (as well as in animal feed), depending on assumptions specified for the *antemortem* inspection[2]. In addition, the SRM inspector, renderer, and MBM transport parameters for healthy slaughter animals will govern processing of non-ambulatory animals.

Finally, if the user chooses to treat non-ambulatory cattle like healthy slaughter animals, tissue from these animals may be available for use in human food, subject to constraints imposed by *antemortem* inspection.

2.1.8 Explicit Modeling of Recycling of Cattle Tissue in Poultry Feed

The simulation model allows the user to specify the proportion of the MBM produced that is used in poultry feed (separate values can be specified for dead and healthy slaughter cattle), and the proportion of poultry litter that is administered to cattle. The model assumes that 100% of infectivity in poultry feed ends up in poultry litter. As a result, the proportion of MBM infectivity that ends up in cattle feed via this pathway is the product of the proportion of MBM sent to poultry feed producers, and the proportion of poultry litter that is used in cattle feed.

2.2 Base Case Assumptions

This section outlines changes made to the base case assumptions used in the earlier risk assessment (1) and implemented in the current analysis. Revisions discussed include those related to the assignment of ambulatory status (Section 2.2.1), those related to *antemortem* inspection (Section 2.2.2), assumptions regarding the amount of infectivity in tonsils (Section 2.2.3), assumptions related to the level of compliance with the feed ban (Section 2.2.4), new assumptions regarding the use of animals for the generation of T-bone steaks and other uses of bone-in-beef (Section 2.2.5), new assumptions regarding the disposition of dead animals (Section 2.2.6), new assumptions regarding the disposition of rendered products (Section 2.2.7), modifications to the assumed proportion of various tissues made available for human

[2] For this analysis, tissue from non-ambulatory animals cannot be used in human food.

consumption (Section 2.2.8), and new assumptions regarding misfeeding (Section 2.2.9). Section 2.2.10 describes the assumed release of infected cattle into the U.S. in the base case scenario.

2.2.1 Assignment of Ambulatory Status (From Cohen and Gray (3) with Modifications)

The revised model now requires specification of ambulatory status probability conditional on whether an animal displays clinical signs of disease. For animals that show no signs, this analysis assumes that the probability of being non-ambulatory, designated $P(NA \mid NS)$, is the same as the unconditional probability of being non-ambulatory, designated *P(NA)*. This latter probability is simply the proportion of cattle in the entire population that are non-ambulatory.

Although data are not currently available, this analysis assumes approximately 1 in 200 animals is nonambulatory. That is, it is assumed that P(NA) is 0.5% and hence that $P(NA \mid NS)$ is 0.5%. As shown in Cohen and Gray (3), this assumption has only a limited impact on the simulation results.

The probability that animals with clinical BSE signs are non-ambulatory, designated $P(NA \mid S)$, can be calculated using Bayes formula. In particular

$$P(NA \mid S) = \frac{P(S \mid NA)P(NA)}{P(S \mid NA)P(NA) + P(S \mid A)P(A)}, \qquad (1)$$

where $P(S \mid NA)$ is the probability that an animal displays clinical BSE signs given that it is non-ambulatory, and $P(S \mid A)$ is the probability it displays clinical signs given that it is ambulatory. The most extensive BSE compliance data have been collected in Europe (4). However, the European surveillance data do not document ambulatory status. Cohen and Gray (3) investigated a range of values for $P(NA \mid S)$ ranging from 8% (base case) to as high as 100% (see Sensitivity Analysis 8 in that report). Their analysis showed that the value assigned to this parameter had only a minor impact on the simulation results.

2.2.2 *Antemortem* Inspection (From Cohen and Gray (3) with Modifications)

Probability of passing inspection for non-BSE factors – For animals with normal ambulatory status, this analysis uses the pass probabilities used by Cohen *et al.* (1). It is assumed here that non-ambulatory animals do not pass *antemortem* inspection. Note that Cohen *et al.* (1) showed that the simulation results are not sensitive to assumptions about the performance of the *antemortem* inspector. In addition, as described below, this analysis assumes that material derived from non-ambulatory animals cannot be used in human food. On the other hand, non-ambulatory status does not affect use of tissue in animal feed.

Probability that antemortem inspector will discover a clinical animal – Cohen *et al.* (1) assumed that the *antemortem* inspector passes (i.e., fails to successfully identify) 10% of all animals with clinical signs of BSE. That is, that report assumed *antemortem inspection* identifies clinical animals with 90% probability. This analysis assumes that it is more difficult for inspectors to identify non-ambulatory animals as having BSE because there is no opportunity to observe their movements. As a result, it is assumed here that the *antemortem* inspector identifies clinical animals as showing BSE signs with 95% probability if the animal is ambulatory, and with 85% probability if the animal is non-ambulatory. That is, non-ambulatory animals with clinical signs are more difficult to discover than clinical animals that are still ambulatory.

Antemortem rules for use of animals in human food – In the base case, an animal can be used in human food so long as it is ambulatory and passes both aspects of the *antemortem* inspection – *i.e.*, 1) the animal must pass the inspection for non-BSE factors, and 2) the inspector does not identify the animal as showing clinical BSE signs.

Antemortem rules for use of animals in animal feed – In the base case, an animal can be used to produce animal feed so long as the inspector does not identify the animal as showing clinical BSE signs.

Disposition of Nonambulatory Animals – As noted in Section 2.1.7, the simulation allows the user to specify that non-ambulatory animals be treated like animals that die prior to being sent to slaughter. In this case, the animals are disposed of "on the farm" with the same probability as dead animals. When disposed of on the farm the BSE agent in the carcass cannot contaminate either animal feed or human food. When non-ambulatory animals are not disposed of on the

farm, this option causes them to be processed in the same way that dead animals are processed when they are not disposed of on the farm (SRM removal rates, rendering reduction technologies, and disposition assumptions for rendered product). However, this analysis assumes that non-ambulatory animals are treated like healthy slaughter animals, although the disposition of the resulting materials is subject to limitations imposed by *antemortem* inspection rules.

2.2.3 Infectivity in Tonsils (From Cohen and Gray (3))

Recent information suggests that bovine tonsils may carry BSE infectivity (5). A pathogenesis study found that inoculating the brains of calves with tonsil tissue from BSE-infected cattle successfully transferred the disease. Specifically, one out of five calves inoculated intra-cerebrally (i.c.) with tonsil from animals 10 months post infection developed BSE. No other time points (6, 18, or 21 months post infection) have resulted in inoculated calves developing BSE (5;6).

The Scientific Panel on Biological Hazards of the European Food Safety Authority estimated from the results of the pathogenesis study that a 50 gram tonsil would contain no more than 0.005 bovine oral ID_{50}s. An analysis by Det Norske Veritas (DNV), using a different assumption for the differential effectiveness of *i.c. vs.* oral exposure, estimated the infectivity in a 50 gram tonsil to be approximately 0.25 bovine oral ID_{50}s (cited in (5)). The corresponding total in a pair of tonsils is 0.5 bovine oral ID_{50}s.

Assuming an incubation period of 36 months, which has been typical in the pathogenesis study, this analysis estimates that at 10 months post infection (when non-zero infectivity in tonsils was observed), total infectivity in an animal to be approximately 250 cattle oral ID_{50}s (see Cohen *et al.* (1)). Hence, the total infectivity in tonsils implied by the DNV calculations amounts to 0.2% of the total infectivity in the entire animal ($0.5 \div 250$ oral ID_{50}s). This analysis assumes that the tonsils maintain this same fraction of infectivity throughout the BSE incubation period. Given the extremely small proportion of infectivity estimated to be present in tonsils, this simplifying assumption can have at most a negligible impact on the simulation results. In order to maintain the same total quantity of infectivity in an animal assumed by Cohen *et al.* (1), this analysis multiplies the tissue-specific fractions for other tissues at each age point by 99.8%.

2.2.4 Feed Ban Compliance Rates (From Cohen and Gray (3) With Modifications)

This analysis uses government surveillance data to estimate probabilities for mislabeling and contamination in MBM and feed production facilities. Mislabeling occurs when a renderer or feed manufacturer incorrectly labels prohibited product as non-prohibited. Contamination occurs when MBM or feed not labeled as containing a prohibited product is tainted with prohibited product. Contamination can occur in mixed facilities (facilities that manufacture product containing prohibited material and product designated as not containing prohibited material on the same production line) and is presumably made worse by incomplete cleanout procedures when production is switched from prohibited to non-prohibited product.

Since the publication of Harvard's November, 2001 BSE risk assessment (7), additional information on compliance with the 1997 feed rule has become available. The U.S. FDA Center for Veterinary Medicine (CVM) has collected and disseminated the state and FDA inspection results for facilities that handle prohibited material (*i.e.*, ruminant derived protein, with some exceptions). This information (see http://www.accessdata3.fda.gov/BSEInspect) quantifies the number of facilities out of compliance with the feed rule and hence serves as a useful starting point for this report's analysis. However, because the U.S. FDA databases do not report the size of these facilities (*i.e.*, total material throughput), an assumption must be made regarding the size of the non-compliant facilities compared to other facilities. For this purpose, this analysis assumes that the non-compliant facilities are the same size on average as facilities not cited for feed rule violations. This assumption is likely to be conservative because inspectors report that smaller firms are more likely to be cited for violations of various sorts than larger ones (personal communication, Neal Bataller, FDA/CVM, May, 2004).

In order to estimate mislabeling and contamination probabilities, this analysis relies on data collected by FDA/CVM[3] prior to September 2003. FDA/CVM data collected prior to September 2003 better detail the nature of the violations discovered, reporting the total number of firms with at least one violation and designating each violation as a case in which: 1) products were not labeled as required, 2) the facility did not have adequate systems to prevent co-mingling, or 3) the facility did not adequately follow record keeping regulations. More recent data report

[3] Compliance program implementation details can be found at http://www.fda.gov/cvm/CVM_Updates/BSE0305.htm.

violations only in terms of the type of action indicated – *i.e.*, Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI). FDA (8) defines these terms[4].

Table 1 reproduces the April 2002 FDA Update (9), the most recent summary reported prior to the September, 2003 change in database and reporting details. The data summarized here are limited to facilities handling prohibited materials.

Table 1
April, 2002 Results of Inspections at Facilities Handling Prohibited Materials

Facility Type	Inspected (N)	Cited for Mislabeling (N)	Cited for Mislabeling Percent	Cited for Commingling (N)	Cited for Commingling Percent
Renderers	171	4	**2.3%**	3	**1.8%**
Feed mills					
Licensed Feed Mills	370	8	2.2%	2	0.5%
NL Feed Mills	1224	55	4.5%	28	2.3%
Total	1594	63	**4.0%**	30	**1.9%**
Other Firms[(a)]	2153	77	3.6%	34	1.6%

Notes:

(a) Other firms include ruminant feeders, on-farm mixers, protein blenders, and distributors

Use of data collected prior to the December 23, 2003 discovery of a BSE case in Washington state is likely to produce conservative compliance estimates because compliance rates have most likely improved in the wake of that discovery. For example, June, 2005 FDA

[4] According to FDA, "An OAI inspection classification occurs when significant objectionable conditions or practices were found and regulatory sanctions are warranted in order to address the establishment's lack of compliance with the regulation. An example of an OAI inspection classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented" (8).

"A VAI inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the Ruminant Feed Ban. These include provisions such as minor recordkeeping lapses and conditions involving non-ruminant feeds" (8).

compliance data (10) indicate that only 1.1% of rendering firms (2 of 176) were cited for any OIA violation. For feed mills, the corresponding figure was 0.1% (3 of 2,331).

The parameters adopted for this report's analysis are shaded in Table 1 and reproduced in Table 2 for the purpose of comparing them with assumptions made in the earlier risk assessment (1).

Table 2
Assumptions for Mislabeling and Contamination

Parameter	MBM Production				Feed Production			
	2003[(a)]		This Analysis		2003[(a)]		This Analysis	
	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case
Probability of Contamination	14%	25%	1.8%	14%	16%	16%	1.9%	16%
Proportion of Prohibited Material Transferred to Non-Prohibited Material per Contamination Event	0.1%	1%	0.1%	0.1%	0.1%	1%	0.1%	0.1%
Mislabeling Probability	5%	10%	2.3%	5%	5%	33%	4%	5%

Notes:

(a) Values from Cohen et al. (1).

Although the base case parameter values reflect several conservative assumptions, Cohen and Gray (3) showed that even substantial modifications to these rates have at most a modest impact on the simulation results (see Sensitivity Analysis #1 in that report). It is therefore likely that any conservative impact resulting from these assumptions would likewise be modest.

2.2.5 Consumption Rates for Bone-in-Beef (From Cohen and Gray (3))

Cohen *et al.* (1) assumed that slaughter facilities do not produce bone-in cuts of beef from animals over 24 months of age[5]. These cuts are potentially important because they may contain spinal cord, dorsal root ganglia (DRG) or both. At the request of USDA-FSIS (3), and based on

[5] Discussed in Cohen et al. (1) Appendix 1 at 2.18.3

the judgment of USDA-FSIS personnel, this analysis has revised these assumptions to reflect use of bone-in cuts of beef from animals 24 months of age and over. In particular, this analysis assumes that for all animals 12 months of age and older, 30% of spinal cord ends up in bone-in-beef (category "bone") when the spinal cord is not removed during processing. This analysis also assumes that for all animals, 30% of DRG is available for potential human exposure as a result of consuming bone-in-beef (category "bone"). These uses may include specific cuts of beef like T-bone steaks and other uses of these bones, including soup and stock production. The use of spinal cord of cattle 30 months of age and older is banned from human consumption (Federal Register / Vol. 69, No. 7 / Monday, January 12, 2004 / Rules and Regulations).

2.2.6 Disposition of Dead Animals

Table 3 details recent estimates of the proportion of animals that are rendered among downers and those that die prior to slaughter.

Table 3
Proportion of Animals Rendered Among Downers and Those That Die Prior to Slaughter

Category	Total Mortality and Downers	Proportion Rendered
	Informa Economics (11)	
Older cattle		
Dairy	584,550	62%
Feedlot	300,000	94.4%
Beef cows	1,025,750	20.7%
Total	1,910,300	44.7%
Calves	2,365,600	27.4%
Calves and older cattle	4,275,900	35.1%
	U.S. FDA (12), Table 2	
All dead cattle under 500 pounds	2,365,000	5%
Dead cattle from feedlots	300,000	90%
Beef cows	1,400,000	10%
Dairy cows	400,000	60%
Total	4,465,000	17%

In response to comments on its initial analysis and the differences between FDA and Informa estimates, FDA substituted new industry data into the analysis and revised its estimate from 17 percent to 33 percent with an upper bound of 42%. FDA acknowledges uncertainty in the estimates. This analysis adopts U.S. FDA's estimate that 42% of cattle that die prior to

slaughter are rendered (p. 58,588 in (13)). This value is considered by FDA to be an upper bound for this parameter.

2.2.7 Disposition of Rendered Materials

The 2003 risk assessment (1) assumed that approximately 30% of prohibited MBM and non-prohibited MBM is either exported or used in pet food and hence is not available to contaminate domestic cattle feed. While 15% to 30% of MBM produced in the U.S. has typically been exported, that proportion dropped substantially in 2004, to 5% of production. Demand abroad for poultry by-product from the U.S. has remained relatively strong. This analysis therefore assumes that 95% of domestically produced prohibited MBM remains in the U.S. and is available for use in animal feed. For non-prohibited product, this analysis assumes that 70% remains in the U.S. and is available for use in animal feed. Table 4 details the assumed disposition of MBM by type of renderer and type of product.

Table 4
Disposition of MBM

	Type of Renderer and Type of MBM					
	Prohibited Ingredient Renderer		**Non-Prohibited Ingredient Renderer**		**Mixed Type Ingredient Renderer**	
	P	**NP[(b)]**	**P**	**NP**	**P**	**NP**
P Feed Producer (excluding poultry feed)	50%	50%	NA[(a)]	50%	50%	50%
NP Feed Producer	0%	10%	NA[(a)]	10%	0%	10%
Mixed Feed Producer	5%	10%	NA[(a)]	10%	5%	10%
Poultry Feed Producer	40%	0%	NA[(a)]	0%	40%	0%
Out (Unavailable to U.S. Cattle)	5%	30%	NA[(a)]	30%	5%	30%

Abbreviations: P – prohibited, NP – non-prohibited

Notes: *(a)* *This analysis assumes no product from a non-prohibited renderer is labeled as prohibited*

(b) *Prohibited ingredient renderers may produce feed that is mislabeled as non-prohibited.*

Finally, of the infectivity that ends up in poultry feed and ultimately in poultry litter (see Section 2.1.8), this analysis assumes that 1% is used in cattle feed, close to an estimate reported by American Proteins, Inc. (personal communication from Kevin Custer, Vice President of American Proteins, to Lisa Ferguson, USDA APHIS, November 15, 2005).

2.2.8 Food Inspector

For animals 30 months of age and older, this analysis assumes that 1% of SRMs are potentially available for human consumption (brain, spinal cord, dorsal root ganglia [DRG], gut, eyes, AMR-derived meat, bone, and trigeminal ganglia [TGG]). This estimate is based on FSIS data on compliance with the regulations related to Specified Risk Materials (SRMs) (http://www.fsis.usda.gov/Fact_Sheets/BSE_Rules_Being_Strictly_Enforced/index.asp).

2.2.9 The Misfeeding Rate

Cohen *et al.* (1) assumed that 1.6% of correctly labeled prohibited feed was administered to cattle (the misfeeding rate), and that the worst case value for this parameter is 15%. More recent data (www.ngfa.org/article.asp?article_id=5460, last viewed June 5, 2005) indicate that the worst case value for this parameter is 5%, i.e., that a rate of 15% is unrealistically pessimistic.

2.2.10 Import of Infected Cattle

This section describes the assumed base case release of infected cattle into the U.S. as the result of importing bovine livestock from Canada.

Assumed Release of Infected Cattle

The release assessment quantifies the rate at which cattle are imported annually from 2007 through 2026 in each of the following categories: slaughter cattle (steers and heifers, cows, bulls and stags, and calves); stockers/feeders; and breeding cattle.

For the purpose of developing parameter input files, each of these groups must be described in terms of their type (BEEF, BEEFREPRO, or DAIRY), gender (MALE or FEMALE), age (in months), the annual rate at which infected animals in this group are imported (Poisson distribution parameter), age at infection (months), age to be slaughtered (or no age, indicating that the imported animals are to be integrated into the U.S. cattle population). Table 5 divides each of the groups defined in the release assessment into groups with each of these characteristics defined. Note that when these groups are divided across genders or into different age groups, the proportions in the two right-most columns are used to apportion the total. The

values in Table 5 represent the assumed import rates for the base case scenario for the year 2007. For other years, the total import rate for animals in the release group is different, resulting in different estimates for the rate at which infected animals are imported. All other entries in the table are the same for other import years. Finally, note that the age groups identified represent a discrete characterization of what is in reality a more continuous set of values. For example, steers and heifers aged 17, 18, and 19 months old are imported, in addition to those aged 16 or 20 months old (groups specified in Table 5).

Table 5
Apportionment of Release Assessment Import Groups

Release Assessment Group	Type	Gender	Age (Months)	Annual Import Rate	Age at Infection (Months)	Age at Slaughter (Months)	Total Imported in Release Group	Gender Fraction	Age Fraction
SLAUGHTER									
Steers and Heifers	BEEF	MALE	16	0.01	1	16	727,802	60%	5%
	BEEF	MALE	20	0.13	1	20	727,802	60%	45%
	BEEF	MALE	24	0.13	1	24	727,802	60%	45%
	BEEF	MALE	30	0.01	1	30	727,802	60%	5%
	BEEF	FEMALE	16	0.01	1	16	727,802	40%	5%
	BEEF	FEMALE	20	0.10	1	20	727,802	40%	50%
	BEEF	FEMALE	24	0.08	1	24	727,802	40%	40%
	BEEF	FEMALE	30	0.01	1	30	727,802	40%	5%
Cows	BEEFREPRO	FEMALE	60	0.02	1	60	115,424	100%	20%
	BEEFREPRO	FEMALE	72	0.04	1	72	115,424	100%	50%
	BEEFREPRO	FEMALE	84	0.02	1	84	115,424	100%	30%
	DAIRY	FEMALE	36	0.02	1	36	173,136	100%	20%
	DAIRY	FEMALE	46	0.06	1	46	173,136	100%	50%
	DAIRY	FEMALE	72	0.04	1	72	173,136	100%	30%
Bulls and stags	BEEFREPRO	MALE	66	0.04	1	66	53,658	100%	100%
Vealers/light calves	BEEF	MALE	4	0.02	1	4	51,286	70%	100%
	BEEF	FEMALE	4	0.01	1	4	51,286	30%	100%
BREEDING									
Dairy cows/heifers	DAIRY	FEMALE	17	0.03	1	none (b)	49,560	100%	100%
Beef cows/heifers	BEEFREPRO	FEMALE	17	0.00	1	none (b)	4,909	100%	100%
Bulls	BEEFREPRO	MALE	20	0.00	1	none (b)	3,087	100%	100%
STOCKER/FEEDER									
All	BEEF	MALE	12	0.09	1	17	189,139	70%	100%
	BEEF	FEMALE	12	0.04	1	17	189,139	30%	100%

Notes

(a) *The scaled import rate is equal to the product of 1) the annual import rate for the release group (*e.g. *727,802 for steers and heifers in 2007); 2) the gender fraction; 3) the age fraction; AND 4) the BSE prevalence rate 0.68 x 10^{-6} in the base case, which equals the expected value for prevalence calculated using the Bayesian birth cohort method UK feed ban data).*

(b) *These animals are integrated into the U.S. cattle population and hence have no definitive age at slaughter. Each month, they might be slaughtered, depending on the slaughter probability assigned their type, age, and gender.*

2.3 Sensitivity Analyses (From Cohen and Gray (3) with Modifications)

As in the 2003 risk assessment (1), this assessment includes a series of univariate analyses to identify potentially important assumptions. These assumptions are conducted by holding all but one set of assumptions equal to their base case values. The set of assumptions to be evaluated are set equal to pessimistic values to see if doing so influences key model predictions – in particular, for this analysis, the predicted number of cattle infected with BSE in the U.S. over a 20-year period.

The sensitivity analyses conducted here evaluate the impact of alternative assumptions for specific parameters identified as influential in the original analysis (1). This assessment also investigates other assumptions, as described below. The goal of this sensitivity analysis was to investigate the extent to which alternative plausible assumptions might increase the estimated risk associated with importing cattle from Canada.

Sensitivity analyses include:

- *Sensitivity 1* – Mislabeling and contamination – This analysis revises the base case values for these parameters to take into account new data on compliance rates. The sensitivity analyses evaluate the impact of these revisions by using the previous base case values from Harvard's October, 2003 report as the worst case values in the current analysis. In particular, it increases the mislabeling rates to 5% for both MBM and feed production. This sensitivity analysis increases contamination rates to 14% (MBM production) and 16% (feed production) (see Section 2.2.4).

- *Sensitivity 2* – Misfeeding – The base case value for this parameters is 1.6%. This analysis investigates the impact of using the pessimistic value of 5% for this parameter (see Section 2.2.9).

- *Sensitivity 3* – The render reduction factor – This analysis changes the distribution of render reduction factors using the worst case assumptions for this parameter from Harvard's October, 2003 report.

- *Sensitivity 4* – The proportion of poultry litter used in cattle feed. The base case value for this parameter is 1%. The sensitivity analysis investigates use of 5% for this parameter.

- *Sensitivity 5* – The prevalence of BSE in Canada – In place of the base case prevalence of 0.68×10^{-6} (the expected value for prevalence calculated using the Bayesian birth cohort method UK feed ban data), the sensitivity analysis uses a value of 3.9×10^{-6} (the expected value calculated using the BSurvE Prevalence B estimate without including feed ban data).

- *Sensitivity 6* – All assumptions from Sensitivity Analyses 1, 2, 3, 4, and 5. In this analysis, all 5 parameters analyzed in the preceding sensitivity analyses are set to their pessimistic values.

3 Results and Discussion (Introduction From Cohen and Gray (3) with Modifications)

Detailed results of this report's analysis appear in Appendix 2. Appendix 2A summarizes the overall results from each simulation, including epidemic statistics (number of animals infected, *etc*.), frequency of different modes of infection, frequency for different modes of death (natural death *vs.* slaughter), the flow of infectivity through the rendering and feed production system, and potential human exposure to the BSE agent (cattle oral ID_{50}s) by tissue type. Appendix 2B contains a series of 12 graphs for each simulation scenario.

The graphs and tables in Appendix 2 summarize distributions for each of the model's output values. Note that the distributions for each scenario arise as the result of modeled stochastic phenomena corresponding to that scenario's assumptions. For example, the base case scenario assumes that 5% of the rendering facilities do not reduce infectivity levels (*i.e.*, they have a render reduction factor of 1.0). However, the proportion of BSE-infected animals actually sent to such facilities varies from simulation trial to simulation trial. As a result of this and other factors that differ from trial to trial, the trial-to-trial results vary, even though the underlying assumptions (in this case, the proportion of animals sent to each type of rendering facility on average) remain the same. Because many of the underlying assumptions are likewise uncertain, this assessment includes sensitivity analyses (see Section 2.3). For example, the 95^{th} percentile estimate for potential human exposure in the base case provides an upper end estimate for this parameter assuming the base case assumptions are valid. However, the sensitivity analyses describe the range of predictions for the number of BSE cases and potential human exposure values associated with alternative plausible assumptions.

Further documentation of the Appendix 2 tables appears in Appendix 3C of Cohen *et al.* (1), although there is one change to the tables in Appendix 2A. Added to the values listed under the "Epidemic Statistics" heading, these tables now list an estimate of R_0, the epidemic's basic reproduction rate (14). Essentially, the value of R_0 is the average number of animals that become infected as the result of each new infected case. If R_0 is greater than 1.0, the prevalence of the disease tends to grow over time. If it is smaller than 1.0, prevalence tends to decrease over time

and eventually, the disease dies out. Section 1.2 of Gray and Cohen (15) explains the estimation of R_0. In brief, this value is estimated as the number of animals that become infected with BSE (excluding the infected animals introduced through import) divided by the number of BSE-infected animals that die during the simulation.

Tables 6a and 6b summarize key results for the base case and sensitivity analyses, showing how alternative (pessimistic) assumptions affect the predicted number of additional new cases of BSE and total human exposure to the BSE agent over the 20-year simulation period.

Table 6a
Total Number of New Infected Cases of BSE During the 20 Years Simulation Period

		Percentiles				
Scenario	**Mean**	**5th**	**25th**	**50th**	**75th**	**95th**
Base Case	21	12	16	19	22	30
S1 – Mislabel and contam.	21	12	16	19	22	30
S2 – Misfeeding	23	12	16	19	23	42
S3 – Render reduction factor	21	12	16	19	23	30
S4 – Poultry litter	22	12	16	19	23	38
S5 – Canadian BSE Prevalence	120	92	100	110	120	180
S6 – All assumptions	150	99	110	130	160	270

Table 6b
Total Potential Human Exposure to BSE (Cattle Oral ID_{50}s) During the 20 Year Simulation Period

		Percentiles				
Scenario	**Mean**	**5th**	**25th**	**50th**	**75th**	**95th**
Base Case	45	1.6×10^{-5}	0.0056	0.041	0.83	260
S1 – Mislabel and contam.	48	7.9×10^{-6}	0.0054	0.041	0.78	260
S2 – Misfeeding	45	1.2×10^{-5}	0.0062	0.044	1.0	260
S3 – Render reduction factor	48	9.6×10^{-6}	0.0055	0.041	0.83	260
S4 – Poultry litter	45	1.6×10^{-5}	0.0060	0.044	0.92	260
S5 – Canadian BSE Prevalence	260	0.20	2.1	60	260	770
S6 – All assumptions	290	0.26	3.1	120	270	840

The base case results (see Tables 6a, 6b, and Section 1 of Appendices 2A and 2B) indicate that over a 20-year period, imports of cattle from Canada are expected to produce a total of 21 BSE-infected cattle in the U.S. (5^{th} percentile = 12 cases and 95^{th} percentile = 30 cases). The simulation predicts that the vast majority of these cases will be imported, while approximately 10% (2.1 cases expected over 20 years, 5^{th} percentile = 0 cases, 95^{th} percentile = 6

cases) will represent secondary cases resulting from exposure of cattle in the U.S. to BSE from the imported cattle. The relatively small number of predicted native U.S. cases reflects the relatively small estimated R_0 value (mean of 0.044, 5^{th} percentile = 0, 95^{th} percentile = 0.25). Population potential human exposure to the BSE agent is expected to total 45 cattle oral ID_{50}s over 20 years.

The sensitivity analysis results indicate that the assumed Canadian BSE prevalence rate is by far the most important source of uncertainty. Use of the pessimistic value for this assumption increases the expected total number of BSE cases from 21 to 120, and the expected number of secondary BSE cases from 2.1 to 12. Total predicted potential human exposure increases from an expected value of 45 cattle oral ID_{50}s over 20 years to 260 cattle oral ID_{50}s over that time period.

Among the other uncertain assumptions analyzed, the misfeeding rate and the proportion of poultry litter used in cattle feed are most influential, although neither of these is nearly as influential as the assumed prevalence of BSE in Canada. Simultaneous use of pessimistic values for all five uncertain assumptions described here results in a total of 150 BSE cases in the U.S., 42 of which are native to this country. Mean human exposure to the BSE agent increases to 290 cattle oral ID_{50}s over 20 years.

The R_0 parameter is an important aggregate measure of the U.S. agricultural system's robustness in the face of potential disease release scenarios because it indicates whether BSE prevalence will tend to grow or whether BSE will die out over time. The average R_0 value for the base case analysis was 0.044. More importantly, the 95^{th} percentile value for this parameter was 0.25, indicating that if the base case assumptions are valid, it is very unlikely that the disease's prevalence will grow over time independently of the import of additional infectivity. That is, it is very unlikely that $R_0 > 1$. Even simultaneous use of pessimistic values for all five assumptions evaluated here yielded the prediction that $R_0 > 1$ is unlikely. Overall, these results indicate that any plausible release of BSE into the U.S. results in only a limited spread of the disease among cattle in this country. Equivalently, the results indicate that in the absence of a continual release of BSE into the U.S., its prevalence will decrease over time, eventually leading to its elimination. From this prediction, it follows that potential human exposure to the BSE agent would be limited.

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Appendix 1 Base Case Parameter File Changes From Earlier Analysis

Appendix 2 Detailed Simulation Output

Appendix 3 Numerical Stability of Simulation Output

Base Case
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	22	30
Total Infected w/o Imports	2.1	0	0	0	0	6
Total Clinical	0.67	0	0	0	1	2
Probability Infected > 0 at End	0.12	0	0	0	0	1
R_0 Parameter	0.044	0	0	0	0	0.25
Mode of Infection						
Maternal	0.094	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2	0	0	0	0	6
Blood	0.0099	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	17	10	13	16	19	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.7	0	1	1	2	4
ID50 Sources						
From Slaughter	9,700	2,100	3,200	6,300	14,000	25,000
From Death on Farm	11,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	120	320	760	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,400	13,000	22,000	34,000
4 To NP MBM - Contamination	0.0028	0	0	0	0	0
5 To NP MBM - Mislabeling	44	0	0	0	2.6	51
6 Out After Rendering	110	0	0	2.6	26	280
7 To Prohibited Feed	900	33	100	280	1,100	2,500
8 To NP Feed - Misdirected	670	10	58	150	550	2,100
9 To NP Feed - Contamination	0.00095	0	0	0	0	0
10 To NP Feed - Mislabeling	39	0	0	0	0.8	50
11 To Blood	0.63	0	0.000042	0.0033	0.19	3.6
12 Out After Feed Production	1,600	110	290	680	1,400	10,000
13 Misfed to Cattle	12	0	0	0	0	26
14 Total to Cattle	31	0	0	0	0.3	28
15 Total Potential to Humans	45	0.000016	0.0056	0.041	0.83	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	13	0	0	0	0	0
Spinal Cord	4.2	0	0	0	0	0
Blood	0.033	0	0	0	0	0.00027
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	3.9E-7	0	0	0	0	0
Contaminated Muscle Meat	0.16	2.8E-7	0.000075	0.0021	0.023	1.4
AMR	0.64	0	0	0.00098	0.0076	0.26
Beef on Bone	1.2	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.6	0	0	0	0	0
Tonsils	0.026	0	0	0	0	0.025

Sensitivity Analysis 1
Pessimistic Assumptions for Mislabeling and Contamination
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	22	30
Total Infected w/o Imports	2.3	0	0	0	0	7
Total Clinical	0.72	0	0	0	1	2
Probability Infected > 0 at End	0.12	0	0	0	0	1
R_0 Parameter	0.049	0	0	0	0	0.27
Mode of Infection						
Maternal	0.095	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2.2	0	0	0	0	6
Blood	0.01	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	17	10	13	16	19	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.8	0	1	1	2	4
ID50 Sources						
From Slaughter	9,600	2,000	3,200	6,000	14,000	25,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	110	310	750	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,300	13,000	22,000	35,000
4 To NP MBM - Contamination	0.0036	0	0	0	0	0.0026
5 To NP MBM - Mislabeling	56	0	0	0.2	26	230
6 Out After Rendering	100	0	0	2.6	26	280
7 To Prohibited Feed	900	31	94	280	1,100	2,500
8 To NP Feed - Misdirected	700	10	57	150	540	2,100
9 To NP Feed - Contamination	0.012	0	0	0	0	0.026
10 To NP Feed - Mislabeling	46	0	0	0	2.6	100
11 To Blood	0.63	0	0.00004	0.0028	0.18	3.7
12 Out After Feed Production	1,600	110	290	700	1,400	10,000
13 Misfed to Cattle	14	0	0	0	0	26
14 Total to Cattle	37	0	0	0	1.2	30
15 Total Potential to Humans	48	7.9E-6	0.0054	0.041	0.78	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	16	0	0	0	0	0
Spinal Cord	4.9	0	0	0	0	0
Blood	0.026	0	0	0	0	0.00031
Distal Ileum	24	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.00015	0	0	0	0	0
Contaminated Muscle Meat	0.15	1.9E-7	0.000073	0.0018	0.022	0.76
AMR	0.7	0	0	0.00098	0.0076	0.28
Beef on Bone	0.81	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.56	0	0	0	0	0
Tonsils	0.026	0	0	0	0	0.016

Sensitivity Analysis 2
Pessimistic Assumptions for Misfeeding
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	23	12	16	19	23	42
Total Infected w/o Imports	4.2	0	0	0	1	21
Total Clinical	0.95	0	0	0	1	3
Probability Infected > 0 at End	0.16	0	0	0	0	1
R_0 Parameter	0.082	0	0	0	0.059	0.56
Mode of Infection						
Maternal	0.12	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	4.1	0	0	0	1	21
Blood	0.011	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	19	10	14	17	20	33
Die on Farm - Render	1.5	0	0	1	2	4
Die on Farm - No Render	2	0	1	1	2	5
ID50 Sources						
From Slaughter	10,000	2,000	3,300	6,700	14,000	25,000
From Death on Farm	13,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,800	120	320	790	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	16,000	2,000	4,500	13,000	22,000	40,000
4 To NP MBM - Contamination	0.0023	0	0	0	0	0
5 To NP MBM - Mislabeling	42	0	0	0	2.6	51
6 Out After Rendering	110	0	0	2.6	26	280
7 To Prohibited Feed	970	33	100	290	1,100	3,100
8 To NP Feed - Misdirected	690	12	59	160	570	2,100
9 To NP Feed - Contamination	0.0014	0	0	0	0	0
10 To NP Feed - Mislabeling	36	0	0	0	2.6	53
11 To Blood	0.64	0	0.000044	0.0035	0.2	3.8
12 Out After Feed Production	1,600	110	290	700	1,500	10,000
13 Misfed to Cattle	45	0	0	0	2.6	100
14 Total to Cattle	64	0	0	0.0015	5.1	130
15 Total Potential to Humans	45	0.000012	0.0062	0.044	1	260
16 Eliminated by AM Inspector	4,400	0	0	0	10,000	20,000
Human Exposure						
Brain	12	0	0	0	0	0
Spinal Cord	4.1	0	0	0	0	0
Blood	0.035	0	0	0	0	0.00044
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	4.8E-6	0	0	0	0	0
Contaminated Muscle Meat	0.16	2.8E-7	0.000092	0.003	0.028	1.4
AMR	0.68	0	0	0.00067	0.007	0.28
Beef on Bone	1.2	0	0	0.00036	0.0077	0.34
Trigeminal Ganglia	0.75	0	0	0	0	0
Tonsils	0.027	0	0	0	0	0.51

Sensitivity Analysis 3
Pessimistic Assumptions for Render Reduction Factor
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	23	30
Total Infected w/o Imports	2.4	0	0	0	0	7
Total Clinical	0.68	0	0	0	1	2
Probability Infected > 0 at End	0.13	0	0	0	0	1
R_0 Parameter	0.053	0	0	0	0	0.28
Mode of Infection						
Maternal	0.094	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2.3	0	0	0	0	7
Blood	0.01	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	18	10	14	16	20	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.7	0	1	1	2	4
ID50 Sources						
From Slaughter	9,700	2,100	3,200	6,100	14,000	25,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,800	180	410	970	1,600	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,300	13,000	22,000	35,000
4 To NP MBM - Contamination	0.0027	0	0	0	0	0
5 To NP MBM - Mislabeling	45	0	0	0	2.6	56
6 Out After Rendering	98	0	0	2.6	26	280
7 To Prohibited Feed	930	56	140	330	1,100	2,500
8 To NP Feed - Misdirected	720	29	84	190	650	2,100
9 To NP Feed - Contamination	0.0014	0	0	0	0	0
10 To NP Feed - Mislabeling	41	0	0	0	2.6	51
11 To Blood	0.64	0	0.000038	0.0029	0.18	3.7
12 Out After Feed Production	1,700	160	380	860	1,600	10,000
13 Misfed to Cattle	12	0	0	0	0	26
14 Total to Cattle	30	0	0	0	0.48	48
15 Total Potential to Humans	48	9.6E-6	0.0055	0.041	0.83	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	15	0	0	0	0	0
Spinal Cord	5.9	0	0	0	0	0
Blood	0.038	0	0	0	0	0.00026
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	2.6E-6	0	0	0	0	0
Contaminated Muscle Meat	0.15	1.9E-7	0.000074	0.0021	0.023	1.4
AMR	0.74	0	0	0.00084	0.0072	0.25
Beef on Bone	0.83	0	0	0.00036	0.0077	0.31
Trigeminal Ganglia	0.49	0	0	0	0	0
Tonsils	0.024	0	0	0	0	0.016

Sensitivity Analysis 4
Pessimistic Assumptions for Recycling of Chicken Litter
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	22	12	16	19	23	38
Total Infected w/o Imports	3.9	0	0	0	1	17
Total Clinical	0.91	0	0	0	1	2
Probability Infected > 0 at End	0.15	0	0	0	0	1
R_0 Parameter	0.078	0	0	0	0.056	0.52
Mode of Infection						
Maternal	0.12	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	3.8	0	0	0	1	17
Blood	0.011	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	19	10	14	17	20	31
Die on Farm - Render	1.4	0	0	1	2	4
Die on Farm - No Render	2	0	1	1	2	5
ID50 Sources						
From Slaughter	10,000	2,100	3,300	6,800	14,000	26,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	120	320	790	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	16,000	2,000	4,500	13,000	22,000	39,000
4 To NP MBM - Contamination	0.0012	0	0	0	0	0
5 To NP MBM - Mislabeling	41	0	0	0	2.6	54
6 Out After Rendering	95	0	0	2.6	26	280
7 To Prohibited Feed	920	33	100	290	1,100	2,700
8 To NP Feed - Misdirected	720	13	59	160	590	2,200
9 To NP Feed - Contamination	0.0026	0	0	0	0	0
10 To NP Feed - Mislabeling	40	0	0	0	2.6	51
11 To Blood	0.67	0	0.000046	0.0033	0.2	3.8
12 Out After Feed Production	1,600	110	290	700	1,500	10,000
13 Misfed to Cattle	18	0	0	0	0	26
14 Total to Cattle	63	0	0	0.00032	3.1	110
15 Total Potential to Humans	45	0.000016	0.006	0.044	0.92	260
16 Eliminated by AM Inspector	4,500	0	0	0	10,000	20,000
Human Exposure						
Brain	13	0	0	0	0	0
Spinal Cord	5	0	0	0	0	0
Blood	0.031	0	0	0	0	0.0004
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	3.7E-7	0	0	0	0	0
Contaminated Muscle Meat	0.15	2.8E-7	0.000074	0.0025	0.028	1
AMR	0.69	0	0	0.00098	0.0072	0.25
Beef on Bone	0.94	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.66	0	0	0	0	0
Tonsils	0.027	0	0	0	0	0.51

Sensitivity Analysis 5
Pessimistic Assumption for Canadian BSE Prevalence
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	120	92	100	110	120	180
Total Infected w/o Imports	12	0	0	2	8	75
Total Clinical	3.8	0	1	3	4	13
Probability Infected > 0 at End	0.52	0	0	1	1	1
R_0 Parameter	0.075	0	0	0.021	0.067	0.42
Mode of Infection						
Maternal	0.54	0	0	0	1	2
Spontaneous	0	0	0	0	0	0
Protein	11	0	0	2	7	73
Blood	0.062	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	100	79	88	96	110	140
Die on Farm - Render	6.9	2	5	6	8	14
Die on Farm - No Render	9.6	4	7	9	11	18
ID50 Sources						
From Slaughter	61,000	30,000	46,000	59,000	74,000	98,000
From Death on Farm	63,000	20,000	40,000	60,000	80,000	120,000
Disposition of ID50s						
1 To Prohibited MBM	9,200	2,700	4,500	6,400	14,000	23,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	85,000	44,000	64,000	80,000	99,000	140,000
4 To NP MBM - Contamination	0.0089	0	0	0	0	0.0026
5 To NP MBM - Mislabeling	220	0	2.6	26	77	1,000
6 Out After Rendering	530	5.1	42	100	360	1,400
7 To Prohibited Feed	5,000	970	2,000	3,200	5,300	14,000
8 To NP Feed - Misdirected	3,700	580	1,400	2,300	3,700	13,000
9 To NP Feed - Contamination	0.0098	0	0	0	0	0.0026
10 To NP Feed - Mislabeling	220	0	2.6	26	57	1,000
11 To Blood	3.7	0.021	0.45	1.8	5.1	14
12 Out After Feed Production	8,700	2,600	4,200	6,100	13,000	22,000
13 Misfed to Cattle	72	0	0	0.08	26	260
14 Total to Cattle	180	0.000034	2.3	26	51	1,000
15 Total Potential to Humans	260	0.2	2.1	60	260	770
16 Eliminated by AM Inspector	29,000	0	20,000	30,000	40,000	60,000
Human Exposure						
Brain	76	0	0	0	0	36
Spinal Cord	28	0	0	0	0	14
Blood	0.18	0	0	0	0.00036	0.69
Distal Ileum	140	0	0	0.01	260	510
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.000037	0	0	0	0	0
Contaminated Muscle Meat	0.86	0.0089	0.045	0.19	1.4	3.4
AMR	4.2	0.0028	0.017	0.071	0.37	10
Beef on Bone	6.3	0.0019	0.017	0.072	0.38	22
Trigeminal Ganglia	3.1	0	0	0	0	1.4
Tonsils	0.15	0	0	0	0.51	0.51

Sensitivity Analysis 6
Pessimistic Assumptions from Sensitivity Analyses 1 to 5
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	150	99	110	130	160	270
Total Infected w/o Imports	42	2	8	17	53	160
Total Clinical	7.4	0	2	3	7	29
Probability Infected > 0 at End	0.74	0	0	1	1	1
R_0 Parameter	0.23	0.018	0.071	0.14	0.35	0.63
Mode of Infection						
Maternal	0.95	0	0	0	1	4
Spontaneous	0	0	0	0	0	0
Protein	41	1	8	17	53	160
Blood	0.067	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	120	84	97	110	130	200
Die on Farm - Render	9.6	3	5	8	11	24
Die on Farm - No Render	13	5	8	10	15	32
ID50 Sources						
From Slaughter	66,000	32,000	49,000	63,000	80,000	110,000
From Death on Farm	77,000	21,000	50,000	61,000	90,000	180,000
Disposition of ID50s						
1 To Prohibited MBM	12,000	3,400	5,500	8,000	16,000	29,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	100,000	46,000	67,000	87,000	110,000	200,000
4 To NP MBM - Contamination	0.038	0	0	0.000044	0.026	0.1
5 To NP MBM - Mislabeling	390	12	54	100	310	1,200
6 Out After Rendering	680	28	83	190	610	2,000
7 To Prohibited Feed	6,300	1,300	2,600	4,000	7,300	17,000
8 To NP Feed - Misdirected	4,700	820	1,800	2,900	4,800	15,000
9 To NP Feed - Contamination	0.088	0	0	0.0008	0.026	0.26
10 To NP Feed - Mislabeling	330	0.0029	26	52	160	1,100
11 To Blood	4.1	0.028	0.55	2.1	5.8	15
12 Out After Feed Production	11,000	3,200	5,100	7,400	15,000	26,000
13 Misfed to Cattle	300	0	26	51	130	1,100
14 Total to Cattle	640	26	56	130	390	2,200
15 Total Potential to Humans	290	0.26	3.1	120	270	840
16 Eliminated by AM Inspector	32,000	10,000	20,000	30,000	40,000	70,000
Human Exposure						
Brain	89	0	0	0	0	75
Spinal Cord	31	0	0	0	0	15
Blood	0.2	0	0	0	0.00063	0.83
Distal Ileum	150	0	0	8	260	510
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.000016	0	0	0	0	0
Contaminated Muscle Meat	0.95	0.011	0.052	0.25	1.5	3.7
AMR	4.1	0.003	0.018	0.075	0.4	10
Beef on Bone	6.5	0.0022	0.017	0.075	0.47	22
Trigeminal Ganglia	3.5	0	0	0	0	3
Tonsils	0.16	0	0	0	0.51	0.53